

# **Annexe B**

Review of NICE, SMC and AWMSG

February 2007

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## **EXECUTIVE SUMMARY**

Cost effectiveness evaluation provides health policy makers information to compare the costs and benefits of different health interventions to aid decisions on resource allocation. This form of evaluation has become an increasingly important tool in health policy planning.

In the NHS, assessments of the cost effectiveness of drugs and medical interventions are carried out to meet three important goals:

- to improve the quality of care provided by the NHS
- to secure value for money in the use of the limited resources the NHS has at its disposal, and
- to ensure that treatments are available uniformly across the country (that is, to eliminate geographical variations in access).

Three national bodies carry out this role in the UK: the National Institute for Health and Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). Any review of the PPRS needs to take account of the role of these bodies.

### **The role of the bodies**

The process by which cost effective evaluation is carried out varies between the three national bodies. NICE assesses both drugs and other healthcare interventions, but it does not consider all drugs, only those that are referred to it by the Secretary of State for Health. NICE has recently introduced a faster process to evaluate high priority drugs (such as those to combat cancer) so that guidance can be issued closer to when the drug becomes available on the market. SMC assesses and makes recommendations on drugs alone, but, unlike NICE, it assesses all new drugs. AWMSG provides advice to the Minister for Health & Social Services on strategic medicines management and prescribing.

Each body attempts to assess the relative cost effectiveness of a drug by estimating the incremental costs and benefits associated with the drug compared to those of an appropriate comparator. Historically, NICE has carried out longer, more detailed assessments of drugs, developing its own cost effectiveness model, while the SMC and AWMSG provide more rapid recommendations based on a review of manufacturers' own models. Costs taken into account are those borne by the NHS and Personal Social Services (PSS) budget – of which the list price of a drug is a significant component. Benefits relate both to extensions of life and improvements in the quality of life and are commonly expressed in terms of Quality Adjusted Life Years (QALYs).

Although the bodies have not been set a formal cost effectiveness threshold, they generally recommend drugs if the incremental cost per QALY is lower than £20,000. Where the cost / QALY is higher than this, the probability of recommendation is lower, although the bodies may still do so on the basis of other factors, such as wider societal costs and benefits.

## Implementation of recommendations

The recommendations of the three bodies are not binding on prescribers. However, for drugs that have been recommended, local health authorities must provide funding within 3 months for all patients for whom the recommendations apply.

The overall picture as regards the implementation of guidance is complex. Prescribing rates generally increase following positive NICE guidance, although in some cases not to the levels anticipated by NICE when the guidance was issued. There is a number of possible reasons for this, including clinical resistance and the difficulties experienced by PCTs in funding expensive new treatments.

In relation to the implementation of negative recommendations, there are difficulties in interpreting the raw prescribing data, since they do not include information on patient indications. However, more detailed assessments that have been conducted lend support to the view that prescribers may not be following NICE guidance in all cases. Furthermore, in Scotland prescribing of drugs for which SMC has recommended against prescription in all indications reached almost £5m in 2005. Non-compliance may be more of an issue in primary care compared with secondary care. Again, there are likely to be various reasons for non-implementation, including limited time to interpret and assimilate guidance, clinical resistance and possibly countervailing influences such as marketing activities.

Despite these problems, guidance does in many cases have an impact on prescribing behaviour. Positive recommendations can quite clearly increase uptake, for example. It follows that where guidance is not available this can inhibit the uptake of cost effective drugs.

## Issues to address

The technical expertise that these bodies bring to bear in conducting cost effectiveness assessments is of world class standard. A number of high profile, independent studies have given positive reviews of NICE in particular. Further evidence is provided by the fact that the assessments of NICE and SMC are used and referenced in all parts of the world.

In the context of increasing pressures on NHS budgets and ever-higher drug development costs we believe it is vital that this expertise be put to the best possible use in ensuring NHS resources are spent cost effectively. We have identified a number of areas to pursue to achieve this. They relate primarily to the remits the three bodies have been given and fall into five high level categories:

- **allowing cost effectiveness evaluation to inform prices directly**, including the use of more sophisticated approaches such as risk sharing agreements and more flexible price structures. Under current arrangements, the bodies are not given the authority to negotiate prices with the industry. They only have the ability to recommend or not to recommend a treatment at the price proposed by the manufacturer
- encouraging more consistent implementation of the **recommendations of the bodies (positive or negative)**. This could be achieved through a variety of measures, such as greater alignment of financial incentives to prescribers with guidance from the bodies and providing

for the possibility of refusing reimbursement where a cost effective price cannot be secured for a product.

- ensuring **all new drugs are assessed** across the UK, perhaps most importantly, **existing drugs are subject to the same level of assessment as new drugs**. This does not always happen under current arrangements with the result that some very high revenue drugs in primary care can cost significantly more than available alternatives without offering additional benefits to patients.
- addressing certain **institutional issues**, such as the need for **greater coordination between the cost effectiveness bodies** and for **earlier engagement between companies and the bodies**, and
- **addressing more technical issues** relating to the principles for assessing cost effectiveness and the determination of maximum thresholds.

## Conclusion

In the interests of patients, it is vital that NHS resources be used cost effectively. Since their creation, NICE, SMC and AWMSG have made a significant contribution to achieving this aim. They have also shown themselves able to adapt to changing needs – NICE's initiation of the STA process being a recent example. We think there is a case for further reform, expanding the role of the bodies so that cost effectiveness assessment informs price setting directly, as a substitute for existing PPRS profit and price controls.

As discussed in Annexes L and M, we think reform in this direction would deliver major value for money benefits to the NHS. We have identified over £500 million of expenditure that we think could be used more cost effectively under our proposed reforms, giving patients better access to the treatments they need and giving companies the right incentives to invest in the most useful drugs in the future.

# 1 INTRODUCTION

- 1.1 The PPRS works in conjunction with a number of other instruments and institutions designed to improve value for money in NHS purchases of branded drugs. Notable amongst these institutions are the three bodies charged with evaluating the cost effectiveness of drugs and other medical interventions in the UK. Any assessment of the need for and effectiveness of the PPRS therefore needs to take account of the role of these bodies.
- 1.2 Accordingly, the aim of this annexe is to present a comparative overview of the activities of the three UK 'cost effectiveness bodies' and assess their performance to date.<sup>1</sup> The annexe also highlights some of the issues that arise when conducting cost effectiveness analysis, which are relevant for considering its possible use as a means of setting pharmaceutical prices directly.<sup>2</sup>
- 1.3 The three bodies that undertake cost effectiveness analysis in the UK are:
- the National Institute for Health and Clinical Excellence (NICE), which operates in England and Wales (and, as of 1 July 2006, by formal agreement in Northern Ireland)
  - the Scottish Medicines Consortium (SMC), which operates in Scotland, and
  - the All Wales Medicines Strategy Group (AWMSG), which operates in Wales.
- 1.4 There is no separate body that undertakes cost effectiveness analysis for Northern Ireland. Historically, the Department of Health, Social Services and Public Safety of Northern Ireland (DHSSPSNI) has drawn on the work done by the existing cost effectiveness bodies where appropriate. Since the establishment of a formal link with NICE in July 2006, however, guidance from NICE is to be implemented in Northern Ireland, though with different lead-in times to England.
- 1.5 The structure of this annexe is as follows:
- Chapter 2 gives a brief overview of cost effectiveness analysis and the rationale for its use in UK healthcare decision making. It also compares the remits of the cost effectiveness bodies in the UK, reviewing the aims of the bodies and how they set out to achieve these aims in practice
  - Chapter 3 provides an overview of the appraisal process, describing how candidates for appraisal are selected, the timing of the assessment process and involvement of key stakeholders

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<sup>1</sup> In the rest of this annexe we refer to these bodies as 'cost effectiveness bodies'. We recognise that the bodies in question have a broad range of responsibilities (such as the improvement of clinical practice). However, we use this general term to signal the fact that our main focus is on their role in assessing the cost effectiveness of medicines and other healthcare interventions.

<sup>2</sup> Options for reform that consider how cost effectiveness analysis could be used to inform price setting directly are considered in Annexe L.

- Chapter 4 discusses the criteria the bodies take into account in assessing the cost effectiveness of drugs and other healthcare interventions
- Chapter 5 provides a summary of the recommendations of each of the bodies to date
- Chapter 6 considers the implementation of decisions across the UK, reviewing available evidence from prescribing data and from the secondary literature, and
- Chapter 7 highlights the main issues we believe need to be addressed to ensure that best use is made of cost effectiveness assessment in the future.

## 2 THE REMITS OF NICE SMC AND AWMSG

2.1 This chapter reviews the various rationales for the creation of NICE, SMC and AWMSG and explores their individual remits in greater detail.

### The rationale for the creation of the cost effectiveness bodies

2.2 There are three principal rationales for the existence of NICE, SMC and AWMSG:

- to improve the quality of care provided by the NHS
- to secure value for money in the use of the limited resources the NHS has at its disposal, and
- to ensure that treatments are available uniformly across the country (that is, to reduce geographical variations in access).

2.3 The NHS has a limited budget with which to secure the best possible health outcomes. In allocating these scarce resources, trade offs need to be made between widely divergent types of healthcare intervention (for example, between drugs in different therapeutic categories and between drugs and other types of healthcare intervention). This implies the need for some form of cost effectiveness assessment of these different interventions, to choose those that create the greatest benefits for a given level of expenditure.

2.4 Box 2.1 provides a summary description of the issues involved in the assessment of cost effectiveness. A more detailed assessment of these issues is set out in Chapter 4.

#### **Box 2.1: Cost effectiveness evaluation**

Cost effectiveness evaluation allows healthcare professionals to compare the costs and benefits of different health interventions in order to choose how to allocate resources between different treatments for different conditions. Decisions which are based on cost effectiveness analysis should in principle be more explicit, transparent and rationally consistent.

One method of comparing the effectiveness of different interventions is through the use of the Quality Adjusted Life Year (QALY) which takes account of the extent to which a medicine prolongs and improves the quality of a patient's life.<sup>3</sup> The number of QALYs produced by a given intervention is calculated as the number of additional years of life produced by a medicine, adjusted to reflect the quality of life. This can then be combined with cost data to estimate the cost incurred in producing an extra year of perfect health (one QALY).

Using cost effectiveness analysis to inform decision making carries a number of potential

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<sup>3</sup> As will be discussed in greater detail in Chapter 4 below, a variety of health outcome measures can be used in economic evaluations, ranging from clear 'final' health outputs (for example, life years gained) to 'intermediate' output measures or surrogate markers (for example, change in blood pressure). Such intermediate measures are of course only relevant inasmuch as they are correlated with final outcomes (that is, improvements to a patient's quality of life and / or length of life). This annexe focuses mainly on QALYs because the cost effective bodies use this health outcome measure in their decisions.

advantages:

- it provides a framework within which to value health gains associated with different interventions and therefore can help to guide priority setting
- it allows comparisons between interventions for the same problem (effectiveness) and for different problems (efficiency) and therefore is a key tool in securing value for money across the health economy.

There are, however, several challenges in the use of cost effectiveness analysis in decision making:

- value for money thresholds are difficult to determine and, arguably, may need to be adjusted to capture social value judgements/concepts of equity (for example, the importance attached to each QALY may vary according to age/context/dependents, etc)
- there are particular challenges for comparing treatments in very different therapy areas, for assessing mild as opposed to severe forms of a disease, or for assessing 'softer' potential benefits such as patient convenience.

The way in which NICE, SMC and AWMSG have addressed these questions is considered in Chapter 4. We recognise that areas of keen debate remain. Some companies feel, for example, that the QALY process is biased towards life saving drugs (that is, it is hard to demonstrate QALY gain in drugs which improve the quality of life for patients suffering from certain types of illness but do not increase their length of life). It should be noted, however, that where these issues do arise they often reflect fundamental problems of a lack of information (evidence that a drug does indeed improve a patient's quality of life) rather than problems created by a particular methodological approach.

2.5 A natural question is whether the assessment of cost effectiveness could be carried out solely by GPs in primary care and consultants in hospitals. However, as highlighted in Annexe A, principal agent problems within the NHS have led to a situation in which prescribers, particularly in primary care, are generally not sensitive to or sometimes even aware of the price of the products they are prescribing. The creation of the three cost effectiveness bodies therefore represents an attempt to secure some influence for the entity that bears the costs of GPs' decisions (the broader NHS) over the use of resources. Ultimately, since access to care and its quality are improved when resources are used efficiently, this role can also be seen as securing influence for the patients who rely on the NHS over the care they receive, particularly those patients that do not have a strong voice and are unable to mobilise themselves.

2.6 In addition to promoting cost effective prescribing, health departments wish to ensure that treatments are available uniformly across the country to ensure equality of access irrespective of location. A further rationale for the creation of bodies producing guidance at a national level is therefore to reduce any geographical variations in access to treatments.<sup>4</sup>

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<sup>4</sup> It should be noted that some variation in patient care is inevitable in a system based on local decision-making.

- 2.7 The bodies also serve as a centralised source of expertise and advice. It is unrealistic to expect healthcare professionals, particularly in primary care, to be able to assimilate and act on all of the latest information on the clinical and cost effectiveness of different interventions. The complexity and sheer volume of information that needs to be analysed in conducting cost effectiveness assessments means that in most cases there are strong efficiency arguments – based on economies of scale – for conducting such assessments at a national level as an adjunct to local level decision making. This provides a third rationale for the existence of the bodies.
- 2.8 It is worth noting that the system, as currently constituted, can sometimes result in a tension between these national bodies and decision makers at a local level. As is discussed below, the bodies attempt to secure cost effective and geographically uniform prescribing through constraining the autonomy of local decision makers, which sometimes leads to resistance on the part of the latter. It should be noted the much of the guidance produced by the bodies is welcomed by NHS organisations and clinicians. The tension occurs when financial pressures make guidance difficult to implement.

### **A comparison of the remits of UK cost effectiveness bodies**

- 2.9 All three UK cost effectiveness bodies, to varying degrees, reflect the high level objectives outlined above. All three bodies carry out cost effectiveness evaluation for medicines to ensure efficient allocation of fixed healthcare resources. In producing national guidance the bodies are also trying to ensure some degree of consistency in prescribing practice and equality of access to medicines across geographic areas. Therefore they have some degree of interest in eliminating postcode prescribing, as discussed in the box below.

#### **Box 2.2: Postcode prescribing**

The avoidance of postcode prescribing was a principal objective in establishing NICE. Local health organisations receive funding which is weighted according to population characteristics to reflect local needs. NICE's role is to ensure that these resources result in equitable access to medicines and technologies. It looks specifically at technologies where prescribing practices may vary across the country. Once guidance has been published by NICE it replaces local recommendations, in an attempt to reduce uncertainty and variation in prescribing practice.

The SMC's policy statement on postcode prescribing states that all NHS boards are required to follow the national implementation plan for unique medicines to ensure they are made available uniformly across Scotland. However, the adoption of medicines where alternative treatments exist will be the decision of local NHS Boards. Treatment for these conditions may vary across board areas where a board can choose one or two medicines from several potential substitutes for inclusion in their formulary.

The AWMSG has made no explicit statement on postcode prescribing. However, in Wales funding must be made available for medicines which have been supported by AWMSG and approved by the minister. This means that approved medicines should be consistently available across Wales.

It should be noted that for each of the bodies, the objective of equitable access to medicines

relates to the respective countries within which they operate, rather than equitable access across the UK. Inevitably, any disparities in access to medicines between the four countries have tended to attract considerable media attention.

2.10 There is a strong degree of commonality in the means by which these bodies seek to meet their objective of improving efficiency and equity in the allocation of healthcare resources. They each issue guidance to prescribers, but are not involved in:

- enforcing the implementation of guidance<sup>5</sup>
- making reimbursement decisions, or
- negotiations relating to the price of medicines.

2.11 However, there are some differences with respect to what is evaluated and the authority to issue guidance. One major difference is that NICE reviews selected drugs and healthcare interventions whereas both SMC and AWMSG only evaluate drugs. Another clear difference is that both NICE and SMC issue guidance themselves while the AWMSG does not make the final decision on guidance.

## **NICE**

2.12 NICE is responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health. Currently NICE produces advice on clinical practice, in the form of technology appraisals (covering England and Wales, and Scotland for part of its output), interventional procedures (covering the whole of the UK) and clinical guidelines (in England and Wales).<sup>6</sup> In addition, it produces guidance from two separate programmes on effective public health practice.

2.13 It is the area of technology appraisals that are particularly relevant for the discussion of cost effectiveness analysis and therefore will be the main focus of this annexe. Besides medicines, they cover devices, devices, diagnostic techniques, surgical procedures and health promotion activities. Clinical guidelines refer to NICE technology appraisals where relevant.

2.14 NICE assesses both drugs and other healthcare interventions. It does not assess all drugs – only those that are referred to it by the Secretary of State as discussed below. Its multiple technology assessments take longer than those of the other bodies, because they are based on a larger and more complex evidence base. Its single technology assessment process is broadly comparable, in terms of its timeline, with the

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<sup>5</sup> However, NICE does have a programme to support the implementation of its guidance, through encouragement and advice.

<sup>6</sup> Technology appraisals issue guidance on the use of new and existing medicines and treatments. Interventional procedures issue guidance on whether interventional procedures used for diagnosis or treatment are safe enough and work well enough for routine use. Clinical guidelines issue guidance on the appropriate treatment and care of people with specific diseases.

Scottish and Welsh drug assessment processes. NICE is perhaps the most respected source of healthcare technology assessments in the world, and is often quoted in other countries' reimbursement decisions.

## **SMC**

- 2.15 Unlike NICE, the SMC only evaluates drugs (rather than other healthcare interventions). A further difference with NICE is that it assesses and makes recommendations on **all** new drugs. That is, it provides advice to NHS Boards and their Area Drug and Therapeutics Committees (ADTCs) across Scotland about the status of all newly licensed medicines, all new formulations of existing medicines and any major new indications for established products (licensed from January 2002). In comparison with NICE drug appraisals, the analysis that informs the SMC decision is less involved and the time frame of the process is shorter. Key differences in the processes of NICE and SMC are discussed in Chapter 3.
- 2.16 Unlike NICE, SMC does not produce clinical guidelines. These are prepared by the Scottish Intercollegiate Clinical Guidelines Network (SIGN). There is no formalised relationship between SMC and SIGN. However, both bodies will draw on each other's work as it relates to their own remit. SMC and SIGN fall under an umbrella organisation in Scotland, the NHS Quality Improvement Scotland (NHS QIS). NHS QIS was established in 2003 as a Special Health Board to act as the lead organisation to promote and improve the quality of healthcare in Scotland.
- 2.17 SMC decisions are highly regarded and the body has managed to establish a strongly collaborative approach with industry throughout its evaluation process.

## **AWMSG**

- 2.18 The AWMSG provides advice to the Minister for Health & Social Services on strategic medicines management and prescribing. AWMSG's remit is perhaps broader than that of NICE as it gives a general steer on prescribing policy to the Welsh Assembly. The system in Wales varies from that elsewhere in the UK in that the final decision over whether or not to recommend a drug is made by the Minister rather than the AWMSG itself. AWMSG seeks to have a 'close dialogue' with both NICE and SMC to avoid duplication of work.

### 3 THE APPRAISAL PROCESS

#### Topic selection

3.1 The process of selecting drugs for assessment varies between England, Scotland and Wales. In England, there is a comprehensive process of topic selection because not all drugs are reviewed whereas SMC evaluates all drugs. AWMSG also adopts a selective approach but the selection process is not as formal as that of NICE.

#### NICE

3.2 Technologies are formally referred to NICE by the Secretary of State for Health. Topic selection before January 2006 relied on the Advisory Committee on Technology Selection (ACTS), hosted by DH. ACTS received suggestions from the National Horizon Scanning Centre, the NHS R&D Forum, the National Prescribing Centre, and occasionally individuals. ACTS then put a short list through to Ministers who consulted on the final selection of drugs to be appraised in that year.

3.3 During 2006, the process changed. NICE is now responsible for managing early stages of topic selection, although DH Ministers retain final approval.<sup>7</sup> Topics come from a number of sources: DH, the National Horizon Scanning Centre, clinical and public health professionals, patients, carers, the general public and suggestions from within NICE itself.

3.4 Topics considered for appraisal undergo a review process involving experts in the topic area, representatives from the public sector, patient and carer representatives. The following selection criteria are used in the process:

- burden of disease (population affected, morbidity, mortality)
- resource impact (that is, cost impact on the NHS or public sector)
- policy importance (that is, whether the topic falls within a government priority area)
- whether inappropriate variation in practice exists across the country, and
- factors affecting the timeliness or urgency for guidance to be produced.<sup>8</sup>

3.5 It has historically been the case that NICE assessments happen later than those of SMC and AWMSG, once evidence has come to light about uncertainty or inconsistency in prescribing behaviour. However, NICE now has a new process for reviewing some technologies in specific disease areas much more quickly – the Single Technology

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<sup>7</sup> This arrangement was officially announced on 18 September 2006. At the same time, to some extent replacing ACTS, seven new 'independent consideration panels' were set up to advise on which topics NICE should produce guidance. Each panel has a speciality subject, for example cancer, 'children, adolescents and maternity' and long-term conditions.

<sup>8</sup> New NICE technology appraisal process: <http://www.nice.org.uk/page.aspx?o=295373>

Appraisal (STA) process. The traditional NICE process is now known as the Multiple Technology Appraisal (MTA) process.

- 3.6 The STA process produces guidance more quickly for selected drugs considered life-saving or otherwise high priority that have already been licensed. It also produces guidance on new medicines close to when they first become available.
- 3.7 All drugs submitted to NICE for appraisal will be assessed to see if they are suitable for this new process. To date, around 28 drugs have been accepted as suitable for the STA process. The assessment of five anti-cancer drugs was begun in November 2005 and NICE reported on four out of the five in late summer and early autumn of 2006. Guidance for one of the four drugs, Herceptin, was issued within three months of its approval for market authorisation. Guidance for the remaining three drugs was issued one or two years after they had received market authorisation.<sup>9</sup>

### **SMC**

- 3.8 The SMC looks at all new medicines at or around launch. There is therefore no formal process for referring medicines to the SMC.

### **AWMSG**

- 3.9 The AWMSG appraises only high cost products, costing over £2,000 per patient per year, and those high cost products with a significant new indication. There is no formal referral process and AWMSG generally selects appraisals itself advised by Local Health Boards (LHBs) and hospital therapeutics committees, Healthcare Commission Wales, patient groups, industry and sometimes the Minister.
- 3.10 AWMSG does not seek to duplicate or compete with NICE's work and therefore does not normally consider appraising a product if NICE intend to publish their appraisal within 18 months of the projected AWMSG appraisal date.

### **Timing of the assessment process**

- 3.11 The NICE MTA process is longer than that of the SMC and AWMSG because NICE creates its own cost effectiveness model, while the other bodies review the models provided by the company. Both SMC and AWMSG acknowledge that there is merit in having a longer, NICE style, process to complement their faster systems.
- 3.12 As mentioned, NICE has recently implemented a new STA process which will enable single new drugs and existing drugs with new indications to be rapidly assessed. Under this process, guidance will be published 6-15 months earlier than under the MTA process. Assessment is faster because NICE asks for a single submission of evidence

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<sup>9</sup> However, this was because they had been in use from some time before being referred to NICE and is not due to delays in the application of the new process.

from the manufacturer, which it reviews rather than developing its own cost effectiveness model and the process for the independent assessment to the final stage of the appeal process moves more quickly.

3.13 The length of these processes is presented in Table 3.1.

**Table 3.1: Timeframe of the assessment process**

<b>CE Body</b>	<b>Time for assessment (average)</b>
NICE	14 months <sup>10</sup> (MTA), 6 -8 months <sup>11</sup> (STA)
SMC	4 months <sup>12</sup>
AWMSG	6 months

### **Bodies that undertake the economic evaluation**

3.14 In all three countries, economic evaluations are undertaken by separate bodies to those that make the final decision.

3.15 Under the MTA process, NICE commissions independent academic centres to review published evidence on the technology, develop a cost effectiveness model and prepare an assessment report. A separate body, The National Coordinating Centre for Health Technology Assessment (NCCHTA) manages the contracts with the independent academic centres on behalf of DH and NICE.<sup>13</sup> Once completed, the review is then combined with comments from the consultees and commentators to form the evaluation report. An independent Appraisal Committee<sup>14</sup> considers the evaluation report and produces an Appraisal Consultation Document. After comments have been received the Committee prepares its Final Appraisal Determination (FAD).

3.16 The STA process is similar, except that the role of the academic centre is to evaluate the cost effectiveness model and other data produced by the company.

3.17 Within the SMC, the New Drugs Committee is a working group that advises and makes recommendations to the SMC on the cost effectiveness of newly licensed products. The NDC uses available information (including the company's cost effectiveness

<sup>10</sup> 14 months is an average. The NICE MTA process lasts at least 54 weeks.

<sup>11</sup> This again is an average. The time taken will vary according to a number factors, such as whether the final decision is appealed.

<sup>12</sup> The SMC process does not include the time allotted to companies to develop their submissions, whereas the NICE appraisal includes this period. The entire process in Scotland is likely somewhat longer.

<sup>13</sup> The NCCHTA is based at Southampton University and is funded by DH. Its principal customer is NICE but it also carries out research for the National Screening Committee, the Chief Medical Officer and the thirteen National Clinical Directors ('Tsars', for major disease areas such as cancer, mental health and heart disease).

<sup>14</sup> This includes NHS health professionals and people who are familiar with the issues facing patients and carers and seeks the views of organisations representing health professionals, patients, carers, manufacturers and government.

submission) to carry out a rapid assessment of the evidence.<sup>15</sup> The SMC considers the NDC's recommendations about the costs and benefits of using the medicine in Scotland before issuing its final advice.

3.18 The Welsh Medicines Partnership (WMP) is the sub-committee of AWMSG that conducts technology appraisals and all related administration for the AWMSG. The WMP report is summarised at the AWMSG meeting and followed by a short Q&A session before the Group retires to make its recommendation to Ministers. Once a decision has been made, the WMP disseminates the ministerial decision across NHS Wales.

### Involvement of stakeholders

3.19 The appraisal process in all three countries involves stakeholders representing groups such as health care professionals, the industry and patient groups as illustrated in Table 3.2 below. In all countries, a variety of channels exist in the consultation process to involve necessary stakeholders.

**Table 3.2: Appraisal process and stakeholder involvement**

<b>NICE process</b>		
<b>Stakeholder Group</b>	<b>Who is involved</b>	<b>Level of involvement</b>
Manufacturer of the product under appraisal and other directly interested consultees	National patient and carer groups	Comment on the scope
	Bodies representing health professionals	Submit evidence
	Manufacturer of the technology	Recommend other consultees
		Comment on appraisal documents
		May appeal against the final decision
Commentators	Manufacturers of comparator products	Comment on evidence
	Research groups in the field	Comment on appraisal documents
Members of public and healthcare professionals		Send feedback after the Final Appraisal Decision is published
<b>SMC process</b>		
<b>Stakeholder Group</b>	<b>Who is involved</b>	<b>Level of involvement</b>
Manufacturer of the product under appraisal and other directly interested consultees	SMC User Group (industry)	No power to influence the decision.
	New Drugs Committee	May discuss and influence the process

<sup>15</sup> SMC assessors undertake an independent literature search, test the assumptions made by the company, and look at health economic data.

	(one industry member)	Note however that two members of the ABPI sit on the main decision-making committee
Members of public and healthcare professionals <sup>16</sup>	Representative Bodies Patient and Public Involvement Group	Opportunity to present evidence Ensure that patient/carer perspective is considered
<b>AWMSG process</b>		
<b>Stakeholder Group</b>	<b>Who is involved</b>	<b>Level of involvement</b>
Manufacturer of the product under appraisal and other directly interested consultees	NHS Industry Forum <sup>17</sup>	Comment on issues referred by the AWMSG, the NHS and industry  Produce guidance and monitor arrangements between the industry and NHS Wales  Note also that two representatives of the manufacturer concerned are present at decision meetings
Members of public and healthcare professionals	Interest groups	Can submit information to AWMSG and MWP prior to appraisal <sup>18</sup>

## Appeals

- 3.20 NICE, SMC and AWMSG each have an internal appeals process for revisiting and reconsidering decisions in the light of fresh evidence. We do not describe appeal processes in detail in this annexe but the broad principles are the same for each body. An appeal can be launched by a range of stakeholders, including manufacturers and bodies representing patient groups and health professionals. Appeals against decisions made by NICE and AWMSG can consider whether the organisation exceeded its power, failed to act in accordance with its process, or made recommendations unsupported by the evidence submitted. In Scotland, the SMC will review a decision on the basis of process or scientific issues. Such appeals are relatively frequent.
- 3.21 In addition, we understand there may be a possibility of a decision made by NICE being taken to judicial review. It concerns the decision in TA111 on four drugs for Alzheimer's (memantine and the three acetylcholinesterase inhibitors: donepezil, galantamine, rivastigmine). In publishing TA111 in November 2006, NICE ruled that the acetylcholinesterase inhibitors should be prescribed only to patients with moderately advanced symptoms of Alzheimer's (but not for those in 'mild' or 'severe' states of the disease) whilst memantine should not be routinely used in the NHS. (This decision had

<sup>16</sup> Submissions cannot be made to the SMC by individual patients/carers for timing reasons.

<sup>17</sup> The NHS Industry Forum is a sub-group of the AWMSG.

<sup>18</sup> Once AWMSG announces technologies to be appraised, patient groups have a 6 week period to submit information to WMP.

already gone through NICE's internal appeals process.) In late November 2006, some of the manufacturers concerned announced that they would seek a judicial review of the decision, focusing on procedural concerns. The companies have reportedly alleged that NICE's process was unfair because NICE refused to disclose a fully working version of the cost effectiveness model used to underpin the decision.

## 4 CRITERIA FOR ASSESSING COST EFFECTIVENESS

- 4.1 The decision making process of NICE, the SMC and the AWMSG is informed by a cost effectiveness evaluation that is based on evidence relating to the clinical effectiveness and cost of the product in question relative to an appropriate comparator.<sup>19</sup> This evaluation is supplemented with other criteria and input from stakeholders.
- 4.2 In this chapter, we describe the ways in which the bodies reach a decision on the cost effectiveness of drugs and other healthcare interventions, considering the factors that are taken into account in principle and how they are applied in practice. We discuss in turn the approaches adopted by the bodies with respect to the choice of comparators, the estimation of costs and benefits, and the application of cost effectiveness thresholds.

### Choice of comparator

- 4.3 Each body attempts to assess the relative cost effectiveness of a drug by estimating the incremental costs and benefits associated with the drug compared to those of an appropriate comparator. Each of the bodies has defined this comparator as the best alternative treatment. In practice this may mean, depending on the drug in question, comparing it to the most clinically or cost effective available treatment or the most widely used treatment (that is, the marginal treatment that would be displaced by the new drug).

### Costs

- 4.4 In relation to costs, all three bodies assess the impact on the NHS budget and Personal Social Services (PSS) budget.<sup>20</sup> These costs comprise the direct cost of the drug (price multiplied by volume) plus net associated healthcare costs (that is, costs created in administering and monitoring the use of the drug minus costs that would otherwise be incurred on other healthcare interventions but are avoided through the use of the drug, such as the costs of surgery or costs saved in changing from injection to oral administration). These healthcare costs may vary between countries.
- 4.5 All three bodies use prices provided by the company in their cost effectiveness evaluations. Companies are required to submit prices relevant to the NHS and PSS. This is normally the list price or drug tariff price. However, occasionally companies may submit a lower price which they intend to offer to the whole of the NHS.<sup>21</sup> If the price submitted does differ from the list price, NICE guidance states that it should be incorporated in sensitivity analysis but that the reference case should be based on list

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<sup>19</sup> However, in practice there are some cases where the scope for formal economic evaluation is limited. For example NICE's TA77 (for *'Insomnia – Newer Hypnotic Drugs'*) did not contain cost benefit analysis as it was not considered practicable.

<sup>20</sup> PSS includes costs of residential care, home help and child protection.

<sup>21</sup> As noted in Annexe A, purchases in secondary care may be based on transaction prices that differ from the list price. The NHS pays the list price of drugs in primary care.

prices.<sup>22</sup> The SMC adopts a similar approach in its assessments, considering reimbursement (list) prices for primary care<sup>23</sup> and contract prices for secondary care.

- 4.6 As discussed in greater detail below, none of the bodies in the UK negotiates on price. That is, a recommendation will be made in respect of the drug in question at the price originally submitted by the company without further iterations.

## Benefits

- 4.7 In relation to health benefits, effects on both mortality and morbidity are assessed. As discussed above, a common approach is to express health benefits in terms of QALYs. (NICE and SMC require that benefits be expressed in terms of QALYs but AWMSG has not made an explicit policy statement on this issue.) The section below discusses QALYs in some more detail.

## QALYs

- 4.8 QALYs attempt to capture the effects of health interventions on patients' length of life and quality of life in a single index. Each year added to a patient's life expectancy by an intervention can be worth up to one QALY. One QALY is a year in an unimpaired state. But a year spent in pain or discomfort, with impaired mobility, subject to anxiety or depression, or unable to undertake usual activities or self-care would be worth less than one QALY.
- 4.9 To determine the fraction of one QALY experienced by a patient during a year of impaired wellbeing, utility weights are applied. Weights are derived from surveys of patients' preferences over health states and translated into an interval scale. Weights may be assessed for single patients or, more usually, averaged over a number suffering from the same condition.
- 4.10 Various methods can be used to elicit preferences. One example is Time Trade-off, in which respondents are asked what proportion of their remaining lifetime they would be willing to sacrifice in return for being relieved of a given health problem. The more life time they are willing to forego in exchange for perfect health, the bigger is the burden attributed to their health state and the lower its utility weight. Patients are asked to consider how their health states compare to 'perfect health' in an attempt to establish a common standard for utility measurements. Methods other than Time Trade-off, such

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<sup>22</sup> Guide to the Methods of Technology Appraisal, NICE, 2004. The reason for this is that there are no obvious constraints on changes to the transaction price once the product has been assessed, unlike the list price, changes to which are constrained by the PPRS. Furthermore, transaction prices in secondary care may vary significantly between hospitals.

<sup>23</sup> Sourced using the Evadis database which is held at the Information Services Division of NHS National Services Scotland.

as Standard Gamble, use other analytical approaches to obtain a measurement framework for QALYs.<sup>24</sup>

- 4.11 A number of enterprises attempt to simplify the measurement of QALYs by providing pre-scored questionnaires for patients to complete. A widely used example is the EQ-5D framework maintained by EuroQoL.<sup>25</sup>

### **Alternative approaches**

- 4.12 QALYs are only one of a range of measures of benefit that can be used in cost effectiveness analysis. Formally, the health economics literature distinguishes between four principle approaches: cost minimisation; cost effectiveness; cost utility and cost benefit analysis.
- 4.13 Cost minimisation uses the same outcome measure, with costs compared to determine the least cost alternative. Cost effectiveness assessment also uses the same outcome measure (for example, a surrogate such as change in total cholesterol), but both costs and the health outcome differ in magnitude. Cost utility analysis attempts to express benefits in terms of generalisable (that is, non disease-specific) patient outcomes (quality and length of life). QALYs and other health related quality of life measures such as Disability Adjusted Life Years (DALYs) and Healthy Life Years Equivalent (HYE) are examples of this approach. Finally, cost benefit analysis translates both costs and benefits into a monetary value. In the rest of this annexe we use 'cost effectiveness' in the broader sense, to refer to any of these alternative approaches.
- 4.14 It should be noted, however, that even if some of these alternatives focus on 'intermediate' output measures or surrogate markers (for example, change in blood pressure) there is a need, in the interests of delivering value for money, to translate them into some form of patient outcome measure that can be compared across therapeutic areas.

### **Non-patient benefits**

- 4.15 Generally the bodies only consider health benefits accruing directly to the patient in question. However, practice may be changing in this respect. In the review of drugs for the treatment of Alzheimer's, for example, NICE considered also effects on the quality of life of carers, in recognition of the important role carers play in the treatment and monitoring of patients with this disease.

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<sup>24</sup> The Standard Gamble method asks patients to choose between a specific disease state and the uncertainty of a treatment with two possible outcomes: the restoration of full health or immediate death. The aim is to find the probability at which people are indifferent between the certainty of un-health and the uncertain outcome of the treatment. One would expect people in worse health states to accept higher probabilities of death following treatment and the probabilities elicited are used to derive QALYs. The method assumes that the risk preferences of individuals or groups are constant and reliable enough to be used to rank health states.

<sup>25</sup> See <http://www.euroqol.org/>

## Information on benefits

- 4.16 Information on health benefits generally come from some form of trials data. The authorities rank the evidential strength of trial data used as an input into the economic evaluation as follows (moving from the strongest to the weakest evidence): level 1 relates to randomised controlled trials; level 2 is controlled observational studies; level 3 is observational studies without control groups; and level 4 considers expert opinion. A difficulty is created by the fact that trials data do not always demonstrate effectiveness relative to the best available alternative. Trials have historically been carried out primarily for licensing purposes and some licensing authorities (notably the FDA) have expressed a preference in the past for trials to be conducted against a placebo. Here again, however, the picture is changing: EMEA, for example seems to be more in favour of head to head trials, in particular for certain types of treatment.<sup>26</sup>
- 4.17 In the absence of head-to-head trials between the new drug and the best available comparator, the manufacturer is required to model the costs and benefits of the new drug with the comparator. This involves creating a model that uses the trial data of the new drug and existing trial data of the comparator to estimate the incremental cost effectiveness of the new drug.

## Comparison of cost effectiveness and use of ICERs

- 4.18 When the assessment has been carried out, a number of outcomes is possible, as set out in the Table 4.1 below.

**Table 4.1: Incremental cost effectiveness of treatment compared to comparator**

		Benefits (Health Outcomes)		
		Better	Same	Worse
Costs	Higher	Trade off	Reject	Reject
	Same	Accept	Trade Off	Reject
	Lower	Accept	Accept	Trade Off

- 4.19 Where the new drug has lower costs and better outcomes than the available alternative, it is said to 'dominate' the comparator and will be accepted. Similarly, where the drug has higher costs and worse outcomes than the alternative, it is said to be 'dominated' by the comparator and will be rejected.

<sup>26</sup> For instance, trials for cancer drugs typically involve giving the patient the next best comparator since to do otherwise would be unethical. At the international level, a process of harmonisation between the regulatory authorities in the US, Europe and Japan began a decade ago. The purpose was to implement a step by step process to harmonise the technical requirements for the registration of pharmaceuticals. The first phase focussed on harmonising the format for submissions; other areas for harmonisation will be progressed as topics are identified. This harmonisation process may have implications for how authorities assess the therapeutic value of drugs in the future.

4.20 These recommendations appear to be relatively uncontentious. It should be noted, however, that if an existing drug is assessed to be dominated through such an analysis, it is not automatically rejected – the recommendation relates only to the use of the new drug. This lack of an automatic ex post assessment of existing drugs (to take into account factors such as new drug entry or indeed an existing drug going off patent) is an important feature of the current system and one that we consider in greater detail in Annexe L.

4.21 More difficult decisions arise where there is a trade off between costs and benefits. In such situations, the bodies will base their recommendation in large part on the 'Incremental Cost Effectiveness Ratio' (ICER) of the drug in question. This ratio takes the following general form:

$$\text{ICER} = \frac{\text{Cost}_{\text{New drug}} - \text{Cost}_{\text{Comparator}}}{\text{Benefit}_{\text{New drug}} - \text{Benefit}_{\text{Comparator}}}$$

4.22 As noted in Box 2.1, the approach generally adopted in the UK for estimating the ICER of a drug is to estimate the cost per QALY of the drug compared with the relevant alternative (that is, the cost incurred in producing an extra year of perfect health). The higher the ICER, the greater the probability that the drug will be rejected.

### **Factors that influence the maximum acceptable ICER**

4.23 None of the bodies has set a single ICER threshold beyond which all healthcare technologies will be rejected, although NICE has been more explicit about the use of ICERs than SMC or AWMSG.

4.24 NICE has stated that where the ICER is below £20,000 per QALY, it will normally recommend the technology on the basis of the cost effectiveness estimate alone.<sup>27</sup> Where the ICER is above this threshold, there will need to be other factors justifying acceptance. Factors that may justify acceptance at a cost / QALY higher than £20,000 per QALY include:

- the degree of uncertainty surrounding the calculation of ICERs<sup>28</sup>
- the particular features of the condition and population receiving the technology (which may relate to the social value judgements discussed below)
- where appropriate, wider societal costs and benefits<sup>29</sup>

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<sup>27</sup> NICE: Guide to the Methods of Technology Appraisal, April 2004.

<sup>28</sup> In practice, we understand that this means that, all other things being equal, the higher the uncertainty surrounding the ICER estimate, the lower the probability that the Appraisal Committee will recommend the drug.

<sup>29</sup> As noted, in the assessment of Alzheimer's drugs, NICE did consider carer benefits. It is not currently allowed to consider broader costs that fall outside the PSS and NHS budgets.

- the innovative nature of the technology (possibly reflecting the interests of the NHS in encouraging the development of medicines that will benefit patients in the long run).<sup>30</sup>
- 4.25 Where the ICER is above £30,000 per QALY, NICE states that these factors will need to be increasingly strong to warrant acceptance of the technology.
- 4.26 In practice, drugs have sometimes been accepted by NICE at ICERs much higher than £30,000 per QALY. Some research has been carried out to establish which criteria have the most impact on the outcome of the NICE appraisal process. This research, and more recent data we have collected as part of the study, is discussed in Box 4.1 below. The conclusions from the study suggest that at higher levels of ICERs, factors such as uncertainty of the cost effectiveness evidence, and burden of disease explain the rejection of some technologies and acceptance of other with a relatively high ICER.

#### **Box 4.1: Modelling NICE decisions**

Work by academics at City University has attempted to shed light on the weight that NICE accords to cost effectiveness evidence versus other factors when making final decisions in Technology Appraisals.<sup>31</sup>

The authors undertook a statistical analysis of the likelihood that NICE would recommend against a product for NHS use. Factors used to explain decisions included:

- incremental cost effectiveness ratios (ICERs) for accepted and rejected treatments
- uncertainty surrounding ICERs
- the availability of alternative treatment options
- the burden of disease on the NHS (number of people affected)
- impact on NHS budgets, and
- factors particular to individual decisions.

The authors found some evidence of a threshold, in that NICE seemed consistently less likely to accept high-cost treatments. However, some drugs were accepted by NICE with ICERs above £30,000. For example, Riluzole was accepted with an ICER of £38,750, and Orlistat with an ICER of £46,000.

Looking at several different models, the variables that best explained observed decisions were the ICER of a drug along with the uncertainty of the ICER and the burden of the disease treated. In the data, the lower the uncertainty surrounding the ICER and the higher the burden of the

<sup>30</sup> This is a more contentious criterion, since it implies that innovations may be rewarded even if they do not provide direct clinical benefits. Again we discuss the merits of this approach in considering options for reform of the scheme in Annexe L. It is not clear to what extent this principle is followed in practice by NICE.

<sup>31</sup> Devlin N and Parkin D (2004), *'Does NICE have a cost effectiveness threshold and what other factors influence its decisions? A binary choice analysis'*, Health Economics, (13).

disease, the greater the probability that a drug would be accepted. So, for example, drugs with relatively low ICERs were sometimes seen to be rejected if there was significant doubt over the value of the therapeutic benefit they offered. An example of the latter is Relenza, a treatment for 'flu, which was rejected for use in the general adult population at an ICER of under £30,000.

In recent published Technology Appraisals and those still under development, the ICERs for eight drugs that have not been recommended for use range from £38,000 (for bortezomib for multiple myeloma) to £370,000 (for bevacizumab and cetuximab in some contexts for metastatic colorectal cancer). Four of these appraisals went through the MTA process and subsequently went to appeal (drugs for Alzheimer's, anaemia, colorectal cancer, and mesothelioma). Two have already lost on appeal (drugs for Alzheimer's in patients with moderate to severe states of the disease<sup>32</sup>, where ICERs ranged from £45,000 to £53,000, and drugs for cancer-induced anaemia with ICERs up to £100,000). The results suggest that cost effectiveness ratios are important but not the only factor behind NICE's decisions.

- 4.27 SMC rarely approves drugs with an ICER above £30,000, but there are exceptions to this rule (for example, in relation to certain orphan drugs). Caution should be used in interpreting the cost/QALY estimates SMC uses because these numbers come from the company. SMC may have made a decision on the basis of a cost/QALY that differed from the company's estimate, but this would not be apparent from the data.
- 4.28 AWMSG has not publicly stated its decision-making criteria. However it has said that it will 'consider all issues' when making a decision. Once the decision is made a summary of reasons is announced along with the decision.<sup>33</sup>

### **Social value judgements**

- 4.29 As discussed in the previous section, basing a decision on a cost/QALY calculation alone may not adequately reflect the views and values of society. In particular, some people argue that preference should be given to certain types of diseases, to people with certain demographic characteristics (for example, age group, income level, those with dependents) or the interaction of these factors.<sup>34</sup> Others may feel that a distinction should be made between those who engage in lifestyles that increase their risk of developing a health condition later in life (for example, unhealthy eating and drinking habits) as opposed to those who may be genetically predisposed to a medical condition. This section discusses the potential implications of such social value judgements for cost effectiveness assessments.

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<sup>32</sup> As mentioned above, some manufacturers have threatened to seek judicial review of NICE's final decision in TA111.

<sup>33</sup> In 2005, four high cost drugs were reviewed and two were not recommended. The cost/QALY estimate for one drug was £47,389 (Liposomal cytarabine); AWMSG noted that there was uncertainty around the ICER and evidence was weak. For the second drug (pegvisomant), the manufacturer submitted a cost/QALY greater than £100,000. AWMSG reestimated the model and arrived at a cost/QALY of more than £300,000.

<sup>34</sup> For example, persons who are high users of the health services not only on average have a poorer health state but also have lower incomes than those with on average with better health states.

4.30 NICE has created a 'Citizens Council' to give it an indication of public attitudes towards such social value judgements. The Council comprises 30 people, drawn from all groups in the population, who meet twice a year to discuss specific ethical issues put to them by NICE.<sup>35</sup> The Council's views are separate from those of NICE, but NICE uses reports from the Council to inform the work of the independent groups and experts who develop NICE guidance for the NHS and to review the methodology used to develop its guidance.

4.31 NICE have developed principles for the use of social value judgements when developing their guidance.<sup>36</sup> The general view that NICE expresses in this document is that priority should not be given based on demographic characteristics (age, gender, ethnicity, socio-economic group, income etc) except where there is clear evidence that such characteristics are clinically relevant. NICE has expressed a similar view in relation to 'self-inflicted conditions':

*"NICE and its advisory bodies should avoid denying care to patients with conditions that are, or may be, self-inflicted (in part or in whole). If, however, self-inflicted cause(s) of the condition influence the clinical or cost effectiveness of the use of an intervention, it may be appropriate to take this into account."*

4.32 A particular area of contention concerning the use of social value judgements in decision making is in relation to so-called orphan and ultra-orphan drugs (those that treat a very small population). This issue is likely to become increasingly important in the future with the development of 'personalised' medicine. It is therefore discussed in greater detail in Box 4.2 below.

#### **Box 4.2: Ultra-orphan and orphan drugs**

The definition of an orphan medicine varies between countries and jurisdictions. The definition given by the European Agency for the Evaluation of Medicinal Products is a medicine licensed for treating or preventing life-threatening diseases affecting fewer than 5 in 10,000 people in the EU. The UK also has a definition for an ultra-orphan drug which is a medicine for the treatment or prevention of a disease affecting fewer than 1,000 people in the UK.

The NICE Citizens' Council took the view that an ICER of up to £40,000/QALY could be justifiable for ultra-orphan treatments depending on the severity of the disease, evidence of health gain, and whether the disease is life threatening. This view, however, seems to fail to take account of the fact that characteristics such as disease severity, health gain and whether a condition is life threatening should already have been taken into account during the assessment process. The relevant question, then, is whether – when all other factors are held equal – it is appropriate to pay more for ultra-orphan drugs (for example, according to some 'rule of rescue'

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<sup>35</sup> The Citizens Council has so far published reports on what NICE should take into account in considering clinical need, the use of personal data by the national Confidential Enquiries, the evaluation of ultra orphan drugs, mandatory public health measures and on the rule of rescue.

<sup>36</sup> Social Value Judgements: Principles for the development of NICE guidance, December 2005.

principle). Over 80 per cent of the Citizen's Council took the view that the rarity of the condition alone was not a reason for pay a premium for a drug.<sup>37</sup>

After consultation and review, NICE concluded that the existing appraisal process will apply to orphan drugs. For certain ultra orphan drugs, though, NICE has suggested that there may be a need to increase the maximum acceptable ICER. This proposal is still undergoing consultation.<sup>38</sup>

The SMC has made a policy statement on orphan drugs. It recognises that clinical trials data may be less well developed for orphan drugs. However more data may be required in other areas to demonstrate cost effectiveness. To accommodate this, orphan drugs may have a review date set which would allow for an additional submission after more trials/audit data had been collected.

AWMSG has stated that orphan drugs might be an area where it may be willing to pay more for drugs and has asked manufacturers to state explicitly in the submission whether a drug has been granted orphan status.

Some have argued that there is little justification for giving preferential treatment to orphan conditions.<sup>39</sup> Special treatment for orphan drugs is given at the expense of patients who suffer from more common conditions and may impose significant costs on an already financially strained healthcare system. What little empirical evidence there is does not provide support for the view that society considers the rarity of a condition in itself as a strong reason to pay premium prices.

In the future, as high cost personalised medicines become more prevalent, the NHS is likely to find it increasingly difficult to give orphan drugs preferential treatment in cost effectiveness assessments.

- 4.33 Some work is being carried out at the University of Sheffield to establish the relative value which society places on health gains to different beneficiaries. This study aims to generate equity weights based on the preferences of members of the general population. This study is expected to report in May 2007.

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<sup>37</sup> Reported in McCabe C., Claxton K., Tsuchiya A., Raftery J. *Orphan drugs revisited*, Quarterly Journal of Medicine. 2006 32: 373 – 377.

<sup>38</sup> The proposal is outlined in the document '*Appraising Orphan Drugs*' dated March 2006, available on the NICE website.

<sup>39</sup> See, for example, McCabe C, Claxton K and Tsuchiya A. *Special status for orphan drugs in health care decision making processes: a wise move?* British Medical Journal, 2005; 331: 1016-1019.

## 5 OVERVIEW OF RECOMMENDATIONS

5.1 This chapter and the next consider the impact that the recommendations of the bodies have on prescribing behaviour within the NHS. This chapter sets out the status of the recommendations of NICE, SMC and AWMSG for different decision makers within the NHS before providing a summary of their recommendations to date. The next chapter then reviews available evidence on the extent to which recommendations are followed in practice.

### Status of recommendations

- 5.2 In considering the status of the recommendations of NICE, AWMSG and SMC it is important to distinguish between their impact on prescribers and on local funding bodies.
- 5.3 The recommendations of the three bodies are not binding on prescribers. Clinicians in England, Scotland and Wales are free to make decisions on whether to prescribe a particular treatment on a case by case basis, although they are expected to take the guidance into account.
- 5.4 In practice, however, clinicians can only prescribe a drug if the local health authority (PCT or health board for example) will fund it. The ability of the health authority not to fund a drug is constrained by the recommendations of the three bodies. In this respect, there is a distinction between NICE and AWMSG on the one hand and SMC on the other.

### Recommendations of NICE and AWMSG

5.5 The decisions of NICE and the AWMSG can be classified into one of three groups as presented in Table 5.1 below.

**Table 5.1: Classification of NICE and AWMSG decisions**

Classification <sup>40</sup>	Funding for implementation
Recommended for general use	Local health authorities must provide funding within 3 months for all patients
Recommended for restricted use	Local health authorities must provide funding within 3 months for the specified circumstances
Not recommended for use	Local health authorities do not have to provide funding for this treatment

5.6 Since January 2002, NHS organisations in England have been required to provide funding and resources for medicines and treatments recommended in NICE technology

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<sup>40</sup> Recommended for general use applies to all licensed indications whereas a restricted recommendation limits the application of the guidance and may refer to a specific licensed indication and/or a patient subgroup.

appraisals within 3 months of publication. If a technology is currently being appraised by NICE then local NHS organisations continue to make decisions on its use locally. If a drug is supported by AWMSG and approved by the minister then LHBs and Trusts must make funding available within 3 months of notification of the ministerial decision.

## Recommendations of SMC

- 5.7 Decisions from SMC have a slightly different classification system in relation to whether or not the drug must be funded by the Local Health Board (Table 5.2):

**Table 5.2: Classification of SMC decisions**

Classification	Funding for implementation
Unique	All NHS Boards must make these drugs available within 3 months of the decision
An advance on alternatives/the same as alternatives	The Area Drugs and Therapeutics Committees within each Board will consider whether to implement
Worse than alternatives	Advise Boards not to use

- 5.8 This system therefore allows for some form of postcode prescribing for specific drugs in Scotland, albeit only for drugs for which there are therapeutic substitutes.

## Status of NICE recommendations across the UK

- 5.9 NICE guidance does not automatically apply in Scotland. However, in Scotland the NHSQIS reviews NICE MTAs and decides whether they should apply (usually finding that they should). NICE guidance is used informally in Wales where there is no statutory obligation to make funding available for NICE guidance. It is the NAW who make the final decision. In Northern Ireland, as of July 2006, NICE guidance applies automatically, although for the time being NHS Boards have 12 to 24 months in which to make funding available, compared to three months in England.
- 5.10 A NICE MTA recommendation will normally supersede that of SMC or AWMSG where the two conflict as the NICE process is thought to be more robust (involving the development of an independent cost effectiveness model) and to reflect a larger evidence base because it takes place at a later stage in the product's lifecycle. NICE STAs, on the other hand, do not have any status in Scotland: SMC recommendations still stand where the two conflict.
- 5.11 It should be noted that in none of the countries is there any obligation on local health authorities not to fund a treatment when the relevant body has made a negative recommendation. Health authorities might be expected to withdraw funding in such a circumstance, but whether they do so in practice will be determined by the balance of clinical and financial pressures they face at a local level.

## Overview of recommendations

5.12 Table 5.3 below provides a summary of decisions on whether drugs were recommended, not recommended or received a restricted recommendation. The data suggest that NICE does not issue negative recommendations as often as SMC. However, the indicator of this in the final column of the table should be interpreted with caution. The SMC reviews all new formulations of existing drugs as well as entirely new products. It would be expected that more new formulations would fail a cost effectiveness test than entirely new products.<sup>41</sup> Nonetheless, the fact that NICE has historically made relatively few negative decisions has led to a perception, whether justified or not, among some NHS stakeholders that we spoke to that the NICE process has led to cost inflation rather than cost containment in the NHS.

**Table 5.3: Summary of NICE, SMC, AWMSG guidance**

	Decisions	Yes	Restricted Yes	No in all indications	% Negative Decisions
<b>NICE</b>	85	39	42	4	4.7
<b>SMC</b>	251	79	92	80	31.9
<b>AWMSG<sup>42</sup></b>	19	59	5	6	31.6

Data: NICE published guidance (2000 to September 2006); SMC guidance (2002 to March 2006); AWMSG guidance (2003 to October 2006).

5.13 This picture has changed somewhat in recent months, with NICE recommending that a number of drugs not be prescribed in any indication. Guidance for paclitaxel (early stage breast cancer) made one such 'blanket no' recommendation. The cost/QALY was £4,726 but NICE did not recommend the drug due to lack of clinical and cost effectiveness evidence in relation to the best available comparator. Out of 15 recent decisions classified as appraisals under development, eight drugs were not recommended in all indications because they were not considered cost effective (most ICER values were higher than £40,000). Of the remaining decisions, three drugs received restricted recommendations and four were recommended in all licensed indications.

### Consistency of recommendations

5.14 Over the period considered above, there were 16 NICE appraisals of drugs that have also been assessed by the SMC, of which 15 came to the same conclusion. SMC has only disagreed with NICE once, in the appraisal of pimecrolimus for mild-to-moderate

<sup>41</sup> A second point relates to the different approaches taken by the two agencies. The SMC operates a 'pass/fail' approach under which a company's case is either 'proven or not proven' based on the case the company itself makes. NICE, in contrast, interrogates the evidence to establish whether, in any circumstance, a treatment might be cost effective and, if so, for which patients. Because NICE's approach is more investigative it is inherently more likely to result in some aspect of an intervention being found to be cost effective than using the SMC approach. Both approaches have their merits.

<sup>42</sup> Nine of the AWMSG appraisals were suspended or withdrawn by the manufacturer and 31 submissions did not meet the criteria for appraisal.

atopic eczema, which NICE recommended as a second-line therapy but which SMC rejected. In this case the NICE decision superseded that of the SMC.

- 5.15 AWMSG will not assess a drug if NICE is scheduled to do so within 18 months. Therefore there have not been any conflicting decisions to date. Occasionally AWMSG will look at a drug after the SMC has done so and it has, rarely, disagreed with the SMC decision, although disagreement tends to centre around orphan drugs.
- 5.16 Out of nine appraisals for the same drug, SMC and AWMSG disagreed on three of them: anagrelide hydrochloride; teriparatide, and adalimumab.<sup>43</sup> For anagrelide SMC rejected the drug while AWMSG accepted it. For teriparatide SMC recommended restricted use while AWMSG recommended for general use. The respective positions of the bodies were reversed for adalimumab.

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<sup>43</sup> Anagrelide (SMC rejected; AWMSG accepted); Teriparatide (SMC restricted use; AWMSG accepted); Adalimumab (SMC accepted; AWMSG (restricted use).

## 6 IMPLEMENTATION OF RECOMMENDATIONS

- 6.1 It is clearly important, in considering how well the UK cost effectiveness bodies meet their aims of improving the allocation of resources, to assess the extent to which their guidance is followed in practice. If advice is not followed then the rationale for carrying out cost effectiveness evaluation is undermined. Each of the bodies therefore has a clear interest in assessing the extent of implementation.
- 6.2 This chapter outlines the arrangements the bodies have in place for monitoring uptake of the guidance they issue before reviewing available evidence on implementation. The main focus is on the implementation of NICE technology appraisals, since this is the focus of most of the empirical literature. There is some consideration of the implementation of SMC guidance.

### Arrangements for monitoring implementation

- 6.3 Compliance with NICE guidance is formally monitored by the Healthcare Commission through its Annual Healthcheck and four-yearly inspections and the Audit Commission and DH on an ad hoc basis. A Healthcare Commission review of medicines management in the acute hospital sector used NICE guidance as one of its indicators in its assessment of hospital trusts. A sample of 22 NICE technology appraisals was used to assess the uptake of NICE guidance. About half of the trusts planned to secure funding for some medicines in the future, while less than 20 per cent had funding in place for all medicines.
- 6.4 NICE has appointed an implementation systems director to collate information on how the NHS uses NICE guidance. The implementation directorate has recently created a new database of information on the implementation and uptake of NICE guidance (Evaluation and Review of NICE Implementation Evidence or 'ERNIE'). Of the 89 Technology Appraisals that had been published as of 1 November 2006, 47 had at least one study on uptake (either commissioned by NICE or in external literature) documented within ERNIE. The directorate also develops tools to help trusts manage the financial impact of guidance such as costing tools and advisory documents.
- 6.5 SMC has undertaken its own work to assess the uptake and implementation of their decisions. Stakeholder organisations are involved in the development of this project such as SMC Patient and Public Involvement Group (PAPI) and the ABPI. The SMC evaluation will focus on the impact of decisions at the local, regional and national level, the budget impact of forecasts and the linkage between utilisation data and clinical information. SMC plans to report on the progress of the project in its next annual report. However, since the implementation of the majority of SMC decisions is the choice of each local Board, there is no formal implementation strategy.<sup>44</sup>

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<sup>44</sup> The exception to this is for 'unique' medicines, for which an implementation plan and treatment protocol are agreed by the SMC.

- 6.6 In Wales, monitoring of all healthcare standards (including the implementation of AWMSG and NICE guidance) is carried out by the Healthcare Inspectorate Wales (HIW) which inspects all NHS bodies in Wales. HIW has published reports on local health boards (LHB) but the assessments to date have not evaluated the uptake of AWMSG guidance.
- 6.7 The rest of this chapter reviews the available evidence on the implementation of recommendations, drawing on the work of the bodies themselves, assessments carried out by third parties and analysis the OFT has conducted as part of this study.

### **Review of available evidence on implementation of NICE guidance**

- 6.8 This section assesses the implementation of NICE guidance at two levels:
- at the PCT level: whether PCTs provide funding for drugs which NICE has approved for use, within the prescribed timetable, and
  - at the prescriber level: whether prescribing behaviour changes following a negative or positive recommendation.

#### **Implementation at the PCT level**

- 6.9 A review in 2005/2006 of all 570 NHS trusts was carried out as part of the Healthcare Commission's programme to report and monitor health service provision in the NHS. All trusts were required to provide a self-assessment of their compliance to conform to NICE guidance: 84.6 per cent reported they were fully compliant and 4.6 per cent did not meet this standard.<sup>45</sup> These findings suggest a high level of compliance among NHS organisations to implement NICE guidance, although an audit of all trusts was not carried out. A recent study by the Audit Commission attempted to verify implementation of guidance among a sample of PCTs and is discussed below.
- 6.10 The research by the Audit Commission assessed the extent to which a sample of PCTs has made funding available for the implementation of NICE guidance and, where they have not, the reasons for non-compliance.<sup>46</sup> Headline findings of the Audit Commission report were that:
- NICE guidance is not implemented systematically throughout the NHS
  - only 25 per cent of the NHS organisations visited could verify that implementation of NICE decisions took place within three months, and
  - 85 per cent of survey respondents said that funds for implementing technology appraisals were insufficient.

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<sup>45</sup> Healthcare Commission report, *'Results of the annual health check 2005/2006'*, 2006.

<sup>46</sup> Audit Commission report *'Managing the financial implications of NICE guidance'*, 2005. PCTs in 10 Strategic Health Authorities were contacted and 27 replied (a response rate of 36 per cent).

- 6.11 The Audit Commission found the following barriers to implementation among NHS bodies:
- lack of money / access to necessary resources
  - lack of time
  - lack of knowledge about guidance
  - resistance to change.
- 6.12 The largest of the perceived problems among NHS bodies was a lack of funding, with 85 per cent of respondents saying that funds available to implement technology appraisals were insufficient. A further 33 per cent of respondents said that NICE had issued guidance in 2002-03 which they were unable to fund due to high costs of implementation and lack of available local funding. Respondents indicated that there were particular difficulties in implementing NICE guidance for high-cost drugs such as drotrecogin alfa for sepsis and etanercept and infliximab for rheumatoid arthritis.<sup>47</sup>
- 6.13 Similar concerns about lack of funding were found in a survey carried out for the Arthritis and Musculoskeletal Alliance (ARMA) and the British Society for Rheumatology in 2005 to identify whether implementation of NICE guidance on anti-TNF $\alpha$  had occurred and whether barriers to implementation were present.
- 6.14 The survey suggested that three years after NICE approval of anti-TNF $\alpha$ , around one third of rheumatologists were unable to prescribe the drug. This proportion was roughly unchanged from a similar survey carried out among rheumatologists in 2003. The majority of respondents identified lack of funding to be the main barrier (either the allocated funds for the year had not been used or PCT had not released funding). Lack of infrastructure, such as lack of nursing support, was identified as another barrier to implementation.<sup>48</sup>
- 6.15 At the PCT level, funding is not hypothecated for the implementation of NICE guidance. Therefore PCTs face a constant challenge of resource allocation and priority setting, with limited funds available for new treatments. The NHS tariff by which hospitals are funded is, however, adjusted to take account of NICE guidance. This implies that funding partly accounts for unexpected health service provision costs arising from NICE guidance. NICE estimates that the cumulative cost of implementing its guidance between 1999 and 2004 was £800 million.<sup>49</sup>

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<sup>47</sup> Respondents were a random sample of 10 strategic health authorities (SHAs): 27 PCTs, 23 acute trusts, 8 mental health trusts and 4 foundation trusts. See Audit Commission report '*Managing the financial implications of NICE guidance*', 2005.

<sup>48</sup> The British Society for Rheumatology and the Arthritis & Musculoskeletal Alliance, *Implementation of NICE Guidance on use of anti-TNF $\alpha$  therapies for adults with rheumatoid arthritis*, 2005.

<sup>49</sup> We understand that this is an estimate of the total net budget impact on the NHS, assuming full implementation of NICE technology appraisal guidance.

- 6.16 The Audit Commission also found that poor financial management arrangements were a key reason for low implementation at the PCT level. Only 26 per cent of PCTs surveyed said that they systematically undertake horizon scanning and only 36 per cent routinely identify cost savings associated with implementing guidance.
- 6.17 The Audit Commission found that where NHS bodies have robust systems for implementing NICE, clinical resistance rather than funding is the biggest barrier to implementation. The report suggests that clinical guidelines tend to be implemented more regularly where there is a 'champion' (usually a clinician) to develop a business case to obtain funds from the PCT. The impact of guidance on prescribing behaviour is considered in the next section.

### **Implementation at the prescriber level**

- 6.18 If NICE guidance is being implemented one would expect to see prescribing practice change in line with recommendations. In this section we consider whether NICE recommendations have been implemented at the prescriber level by assessing the impact of decisions on prescribing behaviour. (It should be noted that any such impact will also reflect the decision of a PCT to fund a treatment or not, so it is not possible to isolate the individual impact of prescriber autonomy). We both review existing research and present the results of analysis carried out for the present study.

#### Overview of primary care prescribing in England of drugs reviewed by NICE

- 6.19 Of over sixty NICE Technology Appraisals of medicines carried out between 2000 and 2005, at least 19 drugs were recommended for use in all licensed indications, 40 were recommended for restricted use and three medicines were not recommended in any indication. This section analyses public data on the prescribing of these medicines in primary care, before and after the NICE guidance was issued.<sup>50</sup>
- 6.20 Two important caveats should be borne in mind in interpreting these data, however. First, since the publicly-available data relate to primary care prescribing, they are of limited use in assessing uptake of drugs used primarily in secondary care.
- 6.21 Second, there is a particular difficulty in interpreting data relating to uptake of restricted recommendations. Where a drug receives a restricted recommendation, it is recommended for one or more specific indications or patient subgroups. The guidance

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<sup>50</sup> We appraise NICE decisions made no later than mid 2005 because 2005 is the latest full year for which official prescription cost analysis (PCA) data is available to gauge usage following recommendations. The number of TAs making positive recommendations for all products and indications covered is not the same as the number of drugs recommended in all uses by NICE during the period. Some individual drugs with multiple indications are covered by more than one Technology Appraisal, each of which may also cover other drugs. In several cases, a drug features in one TA issuing positive recommendations on all drugs and indications covered but is not recommended in another indication considered by another TA. NICE issued more than 19 'blanket yes' TAs between 2000 and 2005. Some of these TAs covered several drugs. Overall the total number of drugs (implicitly) recommended is likely to be somewhat higher than 19.

may apply, for instance, to a specific sub-group of patients at high risk. The recommendation may stipulate the use of the drug as the first choice in therapy (first line treatment) or conversely, the guidance may recommend that the drug only be offered after other treatments have been used (for example, second, third, or fourth line treatment, etc). This can raise problems for the audit and implementation of guidance and the extent to which compliance occurs, as we discuss in interpreting the results below.

### *Drugs recommended in all indications*

- 6.22 We undertook a brief analysis of the uptake of positive recommendations made by NICE in Technology Appraisals, using PCA data for primary-care prescribing in England.
- 6.23 We looked at the 19 drugs for which NICE made at least one positive recommendation and no negative recommendation during the period 2000 to 2005. The aim was not to undertake a detailed analysis of how closely estimations of clinical need published by NICE were met in practice. Rather, the focus is simply on how prescribing evolved in the presence of only positive signals from NICE.
- 6.24 Each drug in the graph below was the subject of one or more TAs during 2000 to 2005 and received positive recommendations for use – though in some cases with caveats or conditions (less binding than 'restrictions' per se but potentially material nonetheless). Furthermore, most of the drugs shown have not been appraised in all their licensed indications and some are undergoing appraisals as of 2006 to 2007. These facts mean that none of the recommendations can be construed as an unreserved 'blanket yes' signal to prescribe. Nonetheless, each drug was the subject of only positive views during the period shown and therefore, other factors being equal, one might expect usage following decisions at least not to fall from prior trends. It is important to note that not all of the 19 drugs considered appear in PCA data because some are used only in secondary care.<sup>51</sup>
- 6.25 Usage is measured by total annual reimbursements ('net ingredient cost' or NIC) paid to community pharmacies for each drug over all presentations. For each drug, the data series begins in the year that NICE guidance was issued. Figure 6.1 presents the following drugs or drug categories that received a positive recommendation: methylphenidate (for attention deficit hyperactivity disorder in children) in 2000; riluzole in 2001; atypical antipsychotics, etanercept and somatropin in 2002; and topical corticosteroids and drugs for insomnia in 2004. To get a sense of impact of NICE guidance, it is useful to compare levels of prescribing with levels anticipated by NICE (as reflecting compliance with the guidance) at the time the guidance was issued.
- 6.26 Five of the seven series in Figure 6.1 show steady but slight increases in prescribing in response to a positive NICE decision – but in each case a decision occurs at least ten years after the drugs concerned were launched, at a point where usage seems to have

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<sup>51</sup> Such omissions include the glycoprotein IIb/IIIa inhibitors, drotrecogin alfa and trastuzumab.

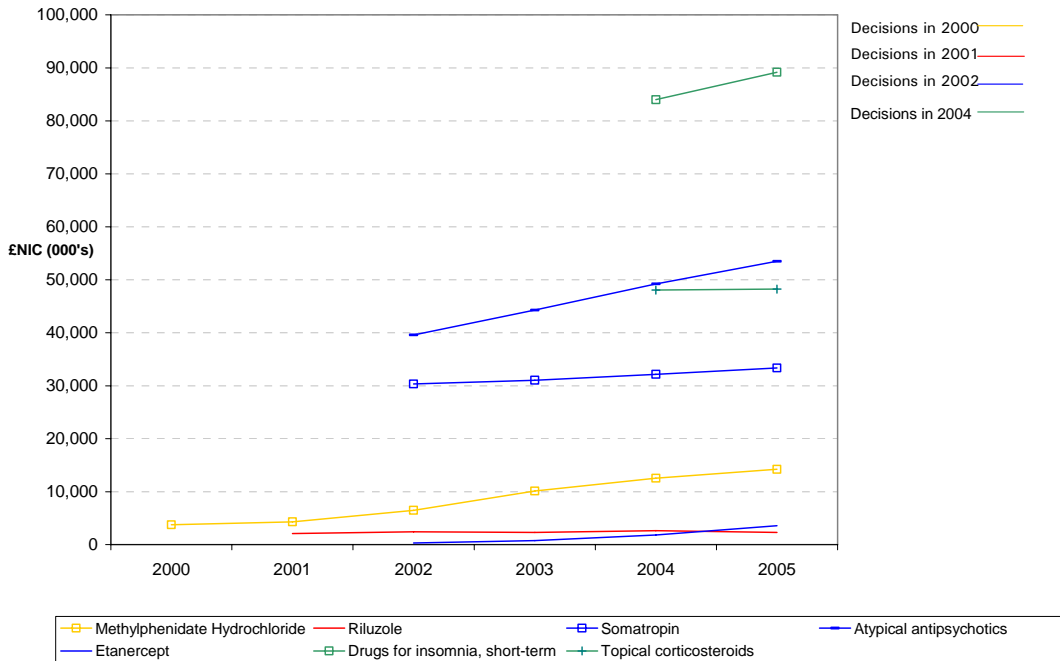
reached a steady state. In 2005 expenditure on somatropin was around £33 million, within the range estimated by NICE (£24 to 42 million). Prescribing of atypical antipsychotics increased following the issuance of NICE guidance, with the level in 2006 (63 per cent of all antipsychotic prescribing) only slightly below NICE expectations (65 per cent).

- 6.27 For the topical corticosteroids and drugs for insomnia, we were unable to compare current trends with the expected level of expenditure, because the guidance did not specify an anticipated budget impact on the NHS. The NIC for topical corticosteroids was £48.2 million in 2005, an increase of £200,000 from the previous year. The NIC amount for drugs for insomnia in 2005 was around £89 million, an increase of about £5 million from 2004. It should also be noted that the guidance for both appraisals was issued in 2004, such that there was only one year of data with which to assess prescribing trends. The data do indicate, however, a slow and steady increase in prescribing over the year.
- 6.28 NICE guidance for riluzole was issued in 2001. Uptake information from the NICE database (ERNI) indicates a level of adoption within primary care which is in line with the NICE recommendation. Trend prescribing of riluzole seems to level off after the positive decision in 2001 – but this occurs after a period of fast growth and may also be explained by uneven diagnosis rates for motor neuron disease, which is a rarer condition than the others concerned by this analysis.
- 6.29 Prescribing for the remaining two drugs - methylphenidate (for attention deficit hyperactivity disorder in children) and etanercept (for rheumatoid arthritis) - responded sharply and positively to NICE recommendations. After NICE guidance for methylphenidate (NICE TA013 2000 decision) was issued, prescribing trends rose sharply, to about £14 million in 2005.<sup>52</sup> NICE estimated spend on drugs that treat rheumatoid arthritis (NICE decision in 2002) ranged from £55 to 75 million. Etanercept – which was only one of the drugs for rheumatoid arthritis - was itself within the NICE estimate and in 2005 its NIC amount was just under £36 million.

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<sup>52</sup> NICE's review of TA013 in TA098 did not anticipate a significant change in prescribing levels after 2004, and in the event there was only a slight increase between 2004 and 2005.

**Figure 6.1: Primary care prescribing in England of drugs recommended by NICE in all indications: net ingredient cost**



Note: Although quarterly data are available annual prescribing levels are shown for clarity and in particular to even out any seasonal fluctuations.

Source: OFT analysis of PCA data.

6.30 The data for the previous graphs, however, are limited to primary care. To have a sense of prescribing trends in secondary care, we reviewed implementation information in the recently launched NICE database, ERNI. This database contains information on the implementation of NICE guidance both in primary and secondary care. Drotrecogin alfa for the treatment of severe sepsis received a positive recommendation in 2004. The NICE estimate of prescribing was £11 to 19 million per year. The uptake data indicate an increase to within this range. In 2004 the NIC amount was just about £5 million but in 2005, this amount had increased to under £12 million, close to the lower bound of NICE estimated levels of uptake. As discussed earlier in this chapter, the Audit Commission found that among the strategic health authorities surveyed, the majority felt they had insufficient funds to cover high cost drugs such as drotrecogin alfa.

*Drugs receiving a restricted (or negative) recommendation*

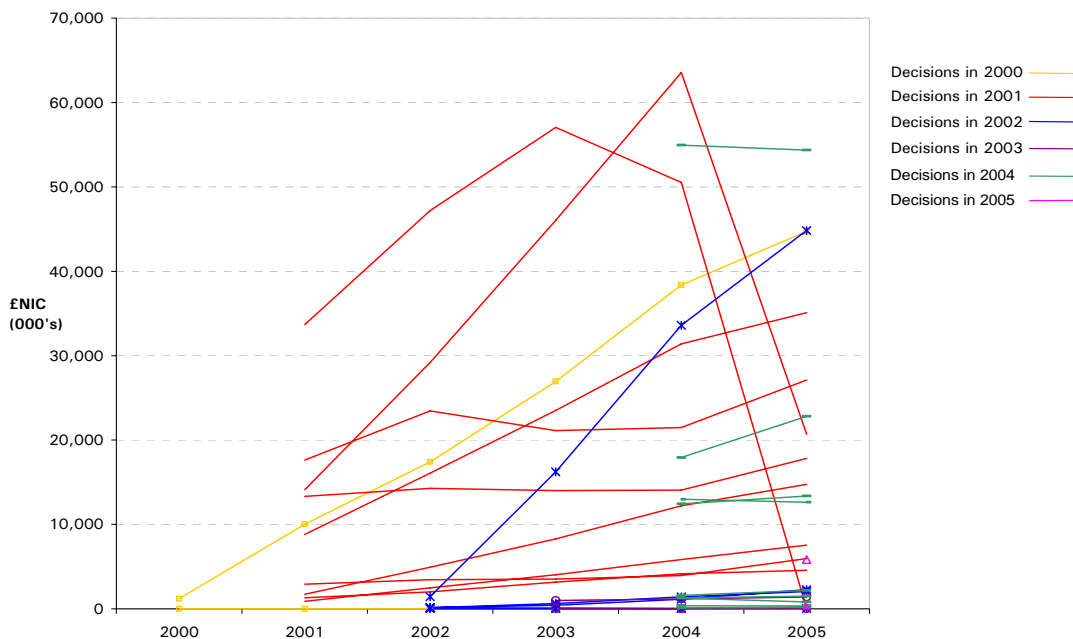
6.31 This section reviews data on the prescribing of drugs in primary care following a negative or restricted NICE recommendation. To get a sense of whether trends in primary care prescribing changed after guidance was issued, prescription cost data

(PCA) from DH were examined. The data suggest that, for most restricted or negative recommendations, prescribing rates increased after NICE guidance was issued.<sup>53</sup>

6.32 Prescribing of 6 (out of 31) drugs fell after the guidance was issued (two of which, as described below, for reasons unrelated to the guidance and the rest by very small amounts). Figure 6.2 presents PCA data on net ingredient costs (NIC) for each of the drugs over the period 2000 to August 2005. In each case, the data series begins in the year in which the NICE guidance was issued. Overall the trend shows rising expenditure during this period.

6.33 It should be noted that in the significant majority of cases, recommendations were restricted, rather than negative in all indications, and that restricted recommendations are sometimes expected to lead to increased levels of prescribing (particularly if the drug is relatively new and the restrictions relatively minor). Therefore, after reviewing prescribing trends, we again assess expenditure against levels anticipated by NICE at the time the guidance was issued.

**Figure 6.2: Primary care prescribing in England against NICE restricted or negative recommendations: net ingredient cost (£000s), 2000 – 2005**



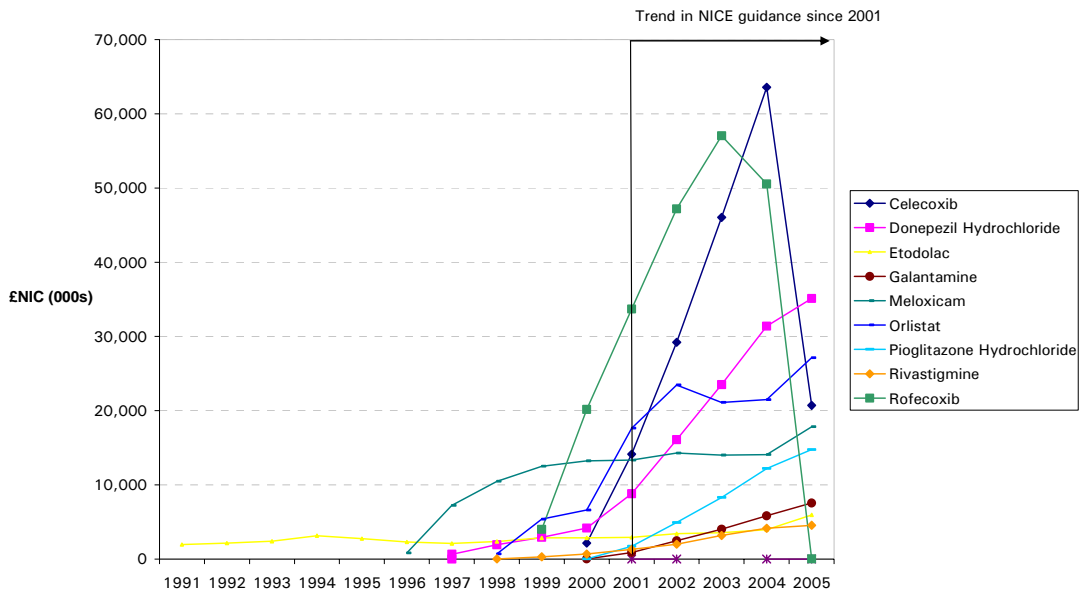
Source: OFT analysis of PCA database

6.34 While the graph shows that for almost all drugs, prescribing rose following a restricted or negative recommendation, this does not in itself demonstrate a change in the trend

<sup>53</sup> Note that a technology appraisal can cover more than one drug. Data to assess prescribing trends based on the NICE negative decisions were available for 31 drugs out of a total of 43.

of prescribing. To better understand whether prescribing behaviour changed, Figure 6.3 presents the trend before and after guidance was issued. For illustration purposes, only decisions made in 2001 are presented but broadly the same trends were observed in the other periods as well.<sup>54</sup>

**Figure 6.3: Primary care prescribing in England against NICE restricted or negative recommendations: net ingredient cost (£000s) in 2001**



Source: OFT analysis of PCA database

6.35 Prescribing trends for almost all drugs increased after 2001. For instance, between 2001 and 2005, donepezil (for the treatment of Alzheimer's) grew from £8,815,000 to £35,115,000 (a 300 per cent increase). Pioglitazone (diabetes) grew from £1,729,000 to £14,750,000 (a 750 per cent increase).

6.36 Expenditure dropped for two Cox II drugs: rofecoxib (100 per cent) and celecoxib (46 per cent) four years after the guidance was issued. However, the drop in both these drugs was not driven by the guidance but rather due to evidence from clinical data which suggested a higher increased risk in cardiovascular events. The manufacturer voluntarily withdrew rofecoxib, also known as Vioxx. As a result, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued advice to patients to contact

<sup>54</sup> We conducted this analysis for each year over the period. Expenditure on almost all the drugs increased over the period. We also conducted the same analysis using quantities (Average Daily Quantities or ADQs) instead of expenditure. It produced very similar results (which largely reflects the fact that, under PPRS, prices of on-patent drugs tend to be stable over time).

their doctor and to arrange for an alternate prescription.<sup>55</sup> The MHRA press release dated December 21, 2004 issued advice to patients taking celecoxib, indicating that patients with established heart disease or at high risk of stroke would have their treatment changed, while for all other patients, alternative treatments would be considered on the basis of their medical history.<sup>56</sup>

- 6.37 Growth in NIC levels before 2001 fluctuated considerably for some drugs and ranged from five per cent to 500 per cent. After 2001, annual percentage increases slowed down but the growth rates for most drugs still ranged from three per cent to 80 per cent.
- 6.38 To assess the impact of NICE guidance, it is necessary to consider the extent to which these increases were in line with NICE estimates. In assessing this, we draw on the initial NICE guidance, our analysis of prescription cost data and an assessment by NICE in 2006 of uptake against five technology appraisals, conducted as part of a Ministerial Industry Strategy Group (MISG) study into variation in uptake of drugs.<sup>57</sup> The analysis here is only of guidance issued in 2001, as this is the year for which there is the largest number of observations and since when a sufficient amount of time has elapsed to allow trends to be observed.
- 6.39 The picture is mixed. For some drugs, prescribing exceeded NICE estimates by a considerable degree. For example, NICE expenditure estimates for orlistat were in the order of £12 million per year. The NIC amounts over the period exceeded £12 million every year and reached £27 million in 2005.
- 6.40 NICE estimated that expenditure on drugs for the treatment for Alzheimer's (donepezil, galantamine, rivastigmine) would be £42 million per year and that it would take several years before a steady state were reached. Prescribing of drugs to combat Alzheimer's disease exceeded NICE's long term estimates within three years of the guidance being issued: in 2005, total expenditure was £47 million.
- 6.41 For other drugs no expenditure estimates were produced by NICE at the time the guidance was issued. An example is Pioglitazone hydrochloride (for the treatment of diabetes), expenditure for which (measured in NIC terms) grew steadily over the period and in 2005 was around £14.7 million.
- 6.42 Overall, prescribing against NICE negative or restricted recommendations reached £351million in 2005. However, as noted above, there is an issue in interpreting these data. Since NICE has very rarely recommended that a drug should not be prescribed in

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<sup>55</sup> Medicines and Healthcare Products Regulatory Agency, 'Immediate withdrawal of rofecoxib (Vioxx/Vioxxacutate), September 30, 2004.

<sup>56</sup> The Medicines and Healthcare Products Regulatory Agency, 'Advice for patients on painkiller/anti-inflammatory – Celebrex', MHRA Press Release, December 21, 2004.

<sup>57</sup> The NICE review assessed uptake of drugs in four therapy areas – obesity, dementia, atypical antipsychotics and severe sepsis – and compared this with estimates provided in the original NICE guidance.

any indication<sup>58</sup> almost all of the drugs considered as part of this analysis were the subject of restricted recommendations (that is, a rejection in some indications but acceptance in others). The public prescribing data do not show the indication for which a drug was prescribed. Therefore it is difficult to assess the extent of prescriber compliance from these data alone: whether physicians reduced prescribing for the indications that were not recommended is unclear. Furthermore, as noted, this analysis does not consider secondary care prescribing.

#### More detailed audit of implementation of guidance for selected drugs

6.43 In this section we review some studies that have attempted to address some of the above problems by conducting more detailed reviews of a limited number of drugs – both in primary and secondary care - using a range of data sources. We consider four studies:

- the National Cancer director's report on the usage of cancer drugs approved by NICE<sup>59</sup>
- an article written for the BMJ by Sheldon et al in 2004 assessing the extent of implementation of NICE guidance, which considered 11 pieces of guidance, 5 of which covered drugs<sup>60</sup>
- research conducted by Abacus in 2005, which looked at 28 pieces of guidance (18 of which concerned drugs) to gauge implementation levels and measure their impact on prescribing practice,<sup>61</sup> and
- research conducted by Roche in 2004 into the uptake of six of its drugs following the publication of NICE guidance.

6.44 The National Cancer Director's second report in 2006 was a follow-up to its first report published in 2004. The first report examined whether patients had appropriate access to drugs approved by NICE. The report found that usage increased following a positive NICE appraisal but that differences between cancer networks existed and were not only due to case mix or cross boundary flows. The main impact on usage was due to constraints in service capacity and differences in clinical practice although variation

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<sup>58</sup> There were only three cases, relating to drugs usually prescribed in hospitals: anakinra, glatiramer acetate and rituximab. In each case NICE recommended against prescribing in all indications but allowed that the drug might be used either as a 'last-line' treatment during clinical studies, meaning that even these decisions are not absolutely negative. Expenditure in primary care on these drugs was just over £2 million: almost all on glatiramer acetate, which is covered by the same risk-sharing scheme put in place by DH for beta interferon. In secondary care, a review of data covering 180 hospital trusts suggests expenditure on the three drugs was £45 million in 2005: anakinra £400,000, glatiramer acetate £750,000 and rituximab was close to £44 million.

<sup>59</sup> Richards M (2006) *Usage of cancer drugs approved by NICE: Report of Review undertaken by the National Cancer Director* Department of Health: London

<sup>60</sup> Sheldon TA, Cullum N, Dawson D, et al. *What's the evidence that NICE guidance has been implemented? Results from a national evaluation using time series analysis, audit of patients' notes and interviews*, BMJ, 2004; 329:999-1006.

<sup>61</sup> 'NICE guidance implementation tracking, data sources, methodology and results': Abacus 2005, available on the NICE website.

appeared to reduce over time. A key recommendation was that cancer networks should develop an action plan for implementation. The follow-up report in 2006 found that while variation still existed it had reduced from previous levels and there had been an increase in the median rate of usage of cancer drugs.

- 6.45 The research by Sheldon et al. scrutinised a random sample of patient records held by PCTs and acute trusts to see whether the guidance was being implemented or not and supplemented this with surveys of trust chief executives and clinical leads. The research found that for certain drugs (taxanes, to combat breast cancer, and orlistat, an anti-obesity drug) use grew rapidly following the publication of NICE guidance. The uptake of drugs to treat Alzheimer's drugs also increased, although this slightly preceded the release of the guidance.
- 6.46 The review of patient records suggested that compliance with the guidance was generally higher in secondary care. Almost all patients were receiving taxanes for the treatment of breast cancer in line with guidance, for example. For drugs that were prescribed in part in primary care, compliance was sometimes weaker, as discussed in Box 6.1.

**Box 6.1: Examples of prescribing in indications not recommended by NICE**

Sheldon et al (2004) finds several cases of widespread 'indication drift' in primary care, when drugs are used beyond indications recommended by NICE. One example concerns the acetylcholinesterase inhibitors for Alzheimer's – donepezil, rivastigmine and galantamine.

As of 2004, these drugs had been assessed by TA19, dated June 2002, which recommended their use only in patients with mild to moderate symptoms of the disease. TA19 recommended against giving acetylcholinesterase inhibitors to patients with severe Alzheimer's, judged as those answering a Mini Mental State Examination (MMSE) with a score of 12 or less. Sheldon and collaborators found that compliance with the NICE guidance was higher in mental health organisations (where 52 to 85 per cent of prescribing was for non-severe Alzheimer's) than in primary care (where only 21 to 46 per cent of usage was for mild-to-moderate cases).

Another drug where prescribing adhered inconsistently to NICE guidance was orlistat for obesity. In TA22, dated March 2001, orlistat was recommended only in patients meeting certain conditions, for example having achieved a degree of weight loss before treatment, having a body mass index (BMI) above a certain level or presenting with complications of obesity such as diabetes.

Prescribing of orlistat fluctuated over the period observed by Sheldon et al but, overall, was found to deviate from the cases recommended in the guidance. Around 40 per cent of patients starting on orlistat during the review period did not meet pre-treatment weight loss criteria and, of those already on treatment, 40 per cent had a BMI lower than that considered by the guidance to justify prescribing.

- 6.47 The Abacus research looked at the impact of NICE guidance on 28 different disease areas. 18 of the technologies reviewed were drugs. Uptake was measured by data on sales volumes from a variety of sources and interviews with clinicians. The study also attempted to estimate what uptake should be if the guidance were fully implemented,

as a benchmark for evaluating implementation. (The study noted, however, that these estimates were based on projections drawn from small sample sizes.)

- 6.48 The study found that implementation varied across disease area, with 12/28 technologies used within reasonable expectations of the guidance (including products with both positive and negative recommendations), 12/28 being under-implemented and 4/28 over-implemented. Within one disease area – colorectal cancer – guidance was found to have an impact on product positioning within the prescribing pathway:
- oxaliplatin was recommended as first line treatment and its usage a first choice agent increased
  - irinotecan was recommended as a second line agent and second line use increased, with first line use decreasing
  - raltitrexed was not recommended and the study found no evidence of prescribing.
- 6.49 The exercise undertaken by Roche examined uptake of NICE guidance relating to a number of treatments manufactured by Roche, including Herceptin, Mabthera and Xeloda, all of which are mainly used in hospitals. In most cases prescribing tended to increase significantly following the publication of NICE guidance. This demonstrates the positive influence of guidance. At the same time, however, it implies that so-called 'NICE blight' – the phenomenon of uptake remaining muted for new drugs until guidance is published – may be a real concern in practice.

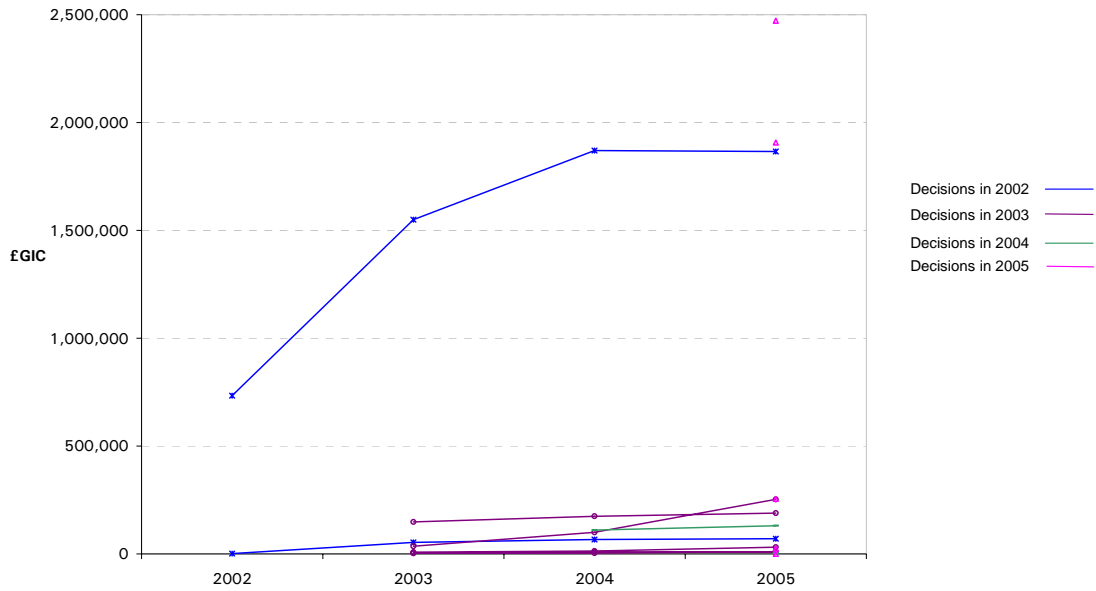
### **Review of evidence on implementation of SMC negative recommendations**

- 6.50 As noted above, part of the difficulty in assessing changes in prescribing trends arises from the fact that until recently most NICE recommendations have been restricted, rather than a negative recommendation in all indications.
- 6.51 In contrast, the SMC has given negative recommendations in all indications on several occasions. Implementation of these negative recommendations is therefore easier to identify from the prescribing data. The graph below shows primary care expenditure in Scotland on drugs for which SMC recommended against prescribing in all indications between 2002 and 2005.<sup>62</sup> Again, in each case, the data series begins in the year in which the SMC guidance was issued. The most striking observation is that prescribing rates in Scotland increased after the guidance was issued.

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<sup>62</sup> We removed drugs for which SMC had initially recommended against prescribing in all indications but had subsequently given a positive recommendation in a new indication. Further we did not include drugs that had received negative recommendations in all indications but had been launched before SMC was established. Therefore we can be clear that SMC has recommended against prescribing all the drugs reviewed in all indications.

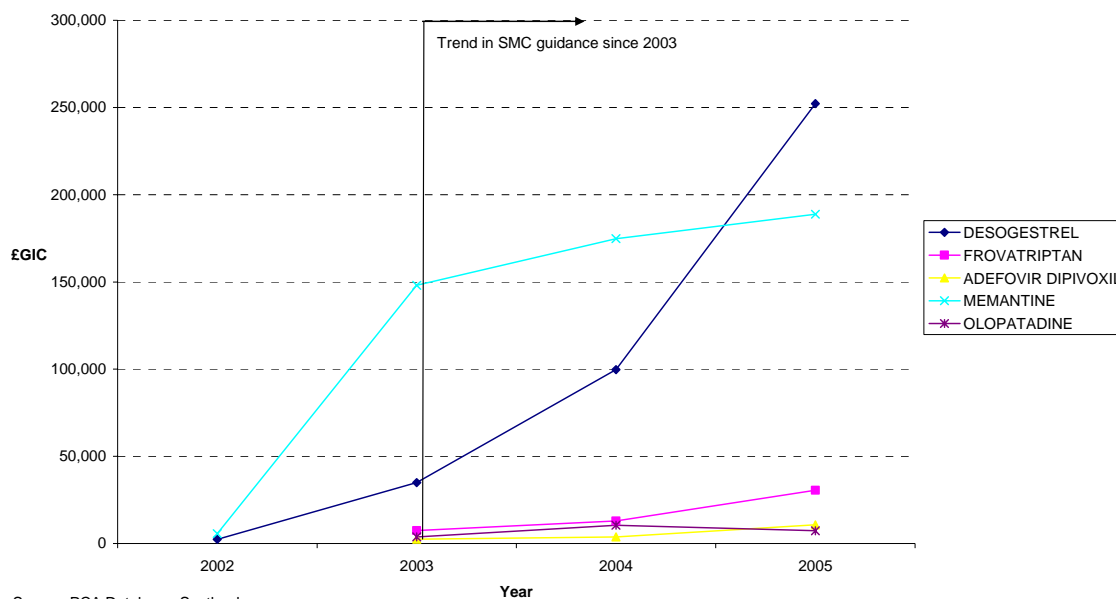
**Figure 6.4: Primary care prescribing in Scotland against SMC negative recommendations: gross ingredient cost (£000s) 2002 - 2005**



Source: OFT analysis of PCA database

6.52 To show any effect on prescribing trends, we also considered prescribing before and after the guidance was issued. For exposition purposes, data from 2003 were selected. These trends are similar to those observed for decisions reached in other years. Figure 6.5 suggests that the trend in costs did not drop (except for one drug) after the guidance was issued. A similar trend was observed in quantity after guidance was issued.

**Figure 6.5: Primary care prescribing in Scotland against SMC negative recommendations: gross ingredient cost (£000s) 2003**



Source: PCA Database, Scotland

6.53 In summary, there has been some prescribing in Scotland even of drugs in respect of which SMC has recommended against prescription in any indication. We estimate that the cost of prescribing drugs that the SMC recommended against on all indications was just under £5 million in Scotland in 2005. We note that we have not provided a comprehensive analysis of uptake of SMC guidance, however. We understand that SMC itself will be producing a more comprehensive analysis later in 2007.

## Summary

6.54 The overall picture as regards the implementation of guidance issued by NICE and SMC is complex. Prescribing rates generally increase following positive NICE guidance, although in some cases not to the levels anticipated by NICE when the guidance was issued. There is a number of possible reasons for this, including clinical resistance and the difficulties experienced by PCTs in funding expensive new treatments.

6.55 In relation to the implementation of restricted and negative recommendations, primary care prescribing rates generally increased following issuance of the guidance, in some significant cases in excess of anticipated expenditure levels, although we recognise that there are difficulties in interpreting the raw prescribing data, since they do not include information on patient indications. However, individual analyses that have been conducted lend support to the view that prescribers may not be following NICE guidance in all cases. In Scotland prescribing of drugs for which SMC has recommended against prescription in all indications reached almost £5 million in 2005. Non-compliance may be more of an issue in primary care compared with secondary

care. Again, there are likely to be various reasons for non-implementation, including limited time to interpret and assimilate guidance, clinical resistance and possibly counterveiling influences such as marketing activities.

- 6.56 Despite these problems, guidance does in many cases have an impact on prescribing behaviour. Positive recommendations can quite clearly increase uptake, for example. It follows that delays in providing guidance can inhibit uptake – the so-called problem of 'NICE blight'. These and other issues are considered in greater detail in the next chapter.

## 7 HIGH LEVEL ASSESSMENT AND ISSUES TO ADDRESS

- 7.1 This section presents a high level assessment of the impact of the UK cost effectiveness bodies and identifies some key issues to address in ensuring best use is made of their work in the future.
- 7.2 The technical expertise that these bodies bring to bear in conducting cost effectiveness assessments is of world class standard. A number of high profile, independent studies have given positive reviews of NICE in particular.<sup>63</sup> Further evidence is provided by the fact that the assessments of NICE and SMC are used and referenced in all parts of the world. Most companies and Government bodies we encountered in conducting our international case studies agreed that the technical competence and credibility of these bodies are unsurpassed anywhere in the world.<sup>64</sup>
- 7.3 In the context of increasing pressures on NHS budgets and ever-higher drug development costs it is vital that this expertise be put to the best possible use in ensuring NHS resources are used cost effectively. We have identified a number of issues to address if this is to be achieved. They relate primarily to the remits the three bodies have been given and fall into five high level categories:
- **the restricted use that is made of cost effectiveness evaluation, in particular the inability to use it to inform prices directly** or to employ more sophisticated approaches such as risk sharing agreements and more flexible price structures
  - **the recommendations of the bodies (positive or negative) may not be fully implemented**, undermining the extent to which cost effectiveness assessments deliver value for money in practice
  - the fact that **not all drugs are assessed** and, perhaps most importantly, **existing drugs are not subject to the same level of assessment as new drugs**
  - **institutional issues**, such as the **need for earlier engagement** between companies and the cost effectiveness bodies and for greater coordination between the cost effectiveness bodies, and
  - some more technical issues relating to the **principles for assessing cost effectiveness and the determination of maximum thresholds**.
- 7.4 We discuss each of these issues in turn.

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<sup>63</sup> See in particular the House of Commons Health Committee 'Review of the National Institute for Clinical Excellence', London, Stationery Office 2002 and Hill S, Garattini S, van Loenhout J, O'Brien B, de Joncheere K 'Technology appraisal programme of the National Institute for Clinical Excellence: a review by the WHO'. London 2003.

<sup>64</sup> Companies in the UK inevitably have a broader range of perspectives, which are reflected below.

## Restricted role for cost effectiveness analysis

- 7.5 NICE, the SMC and the AWMSG are not given the authority to negotiate prices with the industry. They only have the ability to recommend or not to recommend a treatment at the price proposed by the manufacturer.<sup>65</sup> We believe this restriction on their remit undermines the ability of the bodies to secure value for money for the NHS and, increasingly, may work against the interests of companies as well.
- 7.6 The inability of the bodies to discuss prices in making cost effectiveness assessments has a subtle but fundamental effect on the terms of the debate about resource allocation in the NHS. In England in particular, the debate around NICE decisions has tended to focus on 'restricting access' to particular treatments rather than what a fair price for the treatment would be, given the other calls on NHS resources.<sup>66</sup> This in turn, has affected the bargaining position of companies and the NHS.<sup>67</sup>
- 7.7 Decisions by NICE, for example, to reject a product for use in the NHS on cost effectiveness grounds are widely reported in the media and sometimes condemned by interested parties with little regard to the reasoning offered. There are therefore incentives for manufacturers and patient groups to lobby the press to help ensure a drug will get funding. NICE was criticised initially by some commentators for responding to this pressure by rarely giving negative decisions – although we are not aware of evidence to support these assertions in practice.<sup>68</sup>
- 7.8 This picture, however, is changing: as more high cost drugs are reviewed, NICE has begun to say no more often (examples being the recent cancer drugs and drugs to combat Alzheimer's disease, which were discussed earlier in this annexe). SMC, as discussed earlier, has tended to give significant numbers of 'no' recommendations.<sup>69</sup> Given increasing pressures on NHS budgets these trends might be expected to continue. In this context, it is becoming increasingly apparent that current restrictions on the ability to discuss price are unhelpful not just to the NHS but to companies as well. Many companies have told us that they are genuinely uncertain, when submitting a proportion of their submissions, about what the final recommendation will be. This is perhaps unsurprising, given the often cutting-edge nature of the technology involved. However, where the recommendation is likely to be negative, allowing for some

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<sup>65</sup> As noted above, the bodies can and do recommend medicines for restricted use (in the patients who will receive the most benefit).

<sup>66</sup> A recent IPPR survey found that one third of people questioned believed that there should be unlimited access to new drugs irrespective of cost. See IPPR Press Release, 'Most people expect more than the NHS can deliver—new survey data,' September 1, 2006; <http://www.ippr.org/pressreleases/?id=2299>.

<sup>67</sup> Presumably this explains why, when NICE was created, industries were keen that it should not have the power to negotiate prices.

<sup>68</sup> Smith, R. (2000) '*The failings of NICE*', *BMJ*, 321:1363-1364. Cookson, R, McDaid D, Maynard A. (2001), '*Wrong SIGN, NICE mess: is national guidance distorting allocation of resources?*', *BMJ*, 323:743-745.

<sup>69</sup> As noted, the SMC reviews all new formulations of existing drugs as well as entirely new products. It would be expected that more new formulations would fail a cost effectiveness test than entirely new products of the sort NICE tends to assess.

discussion about price before making the final recommendation would represent a mutually beneficial outcome for companies and the NHS.

- 7.9 We believe there may be further benefits from adopting more sophisticated pricing approaches such as risk sharing agreements, which would help deal with the situation in which data may be insufficient at the time of launch to take an informed view on the cost effectiveness of a product (likely to be particularly relevant for the treatment of chronic diseases).<sup>70</sup> Much could also be achieved by allowing for more flexible price structures than at present such as price volume agreements and rebate systems. This would be particularly useful for drugs for which cost effectiveness differs markedly by indication and patient subgroup.<sup>71</sup> These approaches are discussed further in Annexe L. We recognise such approaches will not always be feasible, but consider that they may provide a useful way forward in individual cases.
- 7.10 To the extent to which such measures ensure that price genuinely reflected value to the NHS, we believe they will also help alleviate the effect of more localised rationing decisions which, many companies have suggested to us, can be fairly blunt and focus more on reducing cost in the short term rather than achieving value for money. Using cost effectiveness assessment to inform price directly should give local decision makers greater assurances that drugs prescribed are cost effective at prevailing prices and reduce the need for using volume controls to contain expenditure. We are not assuming that efficient prices alone can solve resource allocation problems within the NHS, but we do think they can make a significant contribution.
- 7.11 In short it is a fundamental contention of this study that better use could be made of cost effectiveness assessment if it were used to inform price setting more directly. We do not discuss the details of alternative approaches here – they are discussed at length in Annexe L, which considers options for reform of the PPRS.

## Implementation of guidance

- 7.12 If cost effectiveness assessment is to be meaningful, it is clearly key that the guidance issued by the bodies should be implemented in practice. As noted in the last chapter, while guidance does have an impact on outcomes, there are problems with implementation.
- 7.13 One recent example – not considered in the last chapter – concerns guidance issued by NICE in relation to the statins - TA94, published in January 2006. The guidance

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<sup>70</sup> Under such an approach, a drug would be recommended at a given price, contingent on claims of clinical effectiveness being realised in practice. This would be assessed through information on the use of the drug in clinical practice. If expected outcomes are not realised, prices would be changed and/or repayments made. While the experience of the risk sharing scheme for Glatiramer acetate has been problematic, this is, as discussed in Annexe L, largely due to the specific nature of the disease and specific contractual issues.

<sup>71</sup> Where this is the case, a higher price could apply for a particular volume of prescriptions, reflecting the patient subgroup for which the drug will be particularly effective, and a lower price for volumes in excess of that.

recommended a substantial increase in statin prescribing for the primary prevention of cardiovascular disease. In its costing estimate for the guidance, NICE assumed that most of the increase would be made up by generic simvastatin. However, TA94 did not stipulate this but rather recommended 'that therapy should usually be initiated with a drug with a low acquisition cost' without mentioning simvastatin by name. Because TA94 was not explicit in recommending simvastatin instead of other chemicals in specific indications, the NICE review of guidance uptake (discussed in the last chapter) was unable to audit prescribing in the same way as for other drugs investigated. As discussed in Annexe M, other statins costing much more than simvastatin enjoy significant levels of prescribing, even though there are doubts about their cost effectiveness at prevailing prices.

- 7.14 Under a model in which cost effectiveness analysis is used to inform pricing, we would anticipate that in most cases (where an acceptable price can be agreed with the manufacturer) this will reduce the need to rely on guidance alone to secure cost effective outcomes: the drug will be cost effective at the price agreed for the treatment in question. However, guidance will still be necessary to support good clinical practice and to deal with those cases in which cost effectiveness differs markedly by indication in ways that cannot be accommodated by more flexible price structures. Further, there will still be a need to ensure drugs are not prescribed when a price cannot be agreed with the manufacturer. Improving prescriber compliance with positive or negative guidance will likely remain an important goal under any revised scheme, as it is under current arrangements.
- 7.15 Discussions with NHS bodies and companies have helped us to identify three mechanisms that could potentially improve implementation:
- financial incentives for prescribers
  - funding for PCOs for positive recommendations, and
  - the possibility of refusing or withdrawing reimbursement for drugs that do not meet acceptable cost effectiveness thresholds.

### **Financial incentives**

- 7.16 In relation to financial incentives, the current Quality and Outcomes Framework (QOF) in the GMS contract is currently not well aligned with NICE guidance. As a result, there may even be incentives for GPs not to follow guidance if there is the potential to receive payments under the GMS contract for doing so. Providing more comprehensive integration of guidance from NICE, SMC and AWMSG into the QOF should improve implementation by prescribers. More 'joined up' incentives across the NHS would also alleviate the burden on prescribers of interpreting large volumes of guidance, by ensuring they are given consistent signals as to what to prescribe and when.

## Funding

- 7.17 In relation to funding, NICE estimate that the cumulative total cost to the NHS of implementing NICE Technology Assessments in 1999-2004 was £800m.<sup>72</sup> PCOs must meet any additional expenditure out of available resources (although these have increased in real terms in recent years). This exposes them to budgetary risks, particularly if a PCO has a particularly high incidence in its local population of a disease the treatment of which is very costly.
- 7.18 Stakeholders have expressed a variety of views on possible solutions. Some NHS stakeholders in England indicated that they would be in favour of system in which additional funding would be provided to PCTs for each new approval. Some companies we spoke to were in favour of a system of hypothecation, ensuring PCO resources were ring fenced to fund new guidance by SMC, NICE and AWMSG. Cookson et al (2001) recommended that NICE should discipline its decisions by managing a fixed-growth budget for new technologies (distributed across PCTs on a needs basis) within which guidance would be prioritised.
- 7.19 These options are part of a broader debate of whether there should be a fixed drugs budget, which we discuss in some detail in Annexe L.

## Refusing reimbursement

- 7.20 For drugs that do not meet acceptable cost effectiveness thresholds – and where the company in question is unwilling to adjust price accordingly – a further option is to refuse or withdraw reimbursement altogether. This is of course a last resort option, but it is important that it be available – where negative guidance alone would not be followed by prescribers - to ensure that such negative assessments are not simply ignored.
- 7.21 This explains why, as discussed in Annexe K, almost all price negotiations are underpinned by a decision as to whether to reimburse a drug or not. In most cases, reimbursement is not refused, because companies and payers are able to reach a mutually acceptable position on price. The threat of withdrawing reimbursement helps ensure this outcome can be achieved, but under such an approach it is particularly important, in the interests of maintaining the stability of investment incentives, that pricing and reimbursement institutions have the confidence of companies and are bound by fair and transparent rules and procedures.
- 7.22 Again, options for reform in relation to reimbursement decisions, and institutional implications, are considered in Annexe L.

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<sup>72</sup> We are not aware of similar estimates having been conducted for the guidance of SMC and AWMSG.

## Drug coverage and ex post review

7.23 One of the key issues to be addressed in maximising the effectiveness of the bodies relates to drug coverage – which drugs are reviewed and, perhaps most importantly, at what stage in their life cycle.

### Drug coverage

7.24 Unlike SMC, NICE does not look at all drugs, only those which are referred to it. This may have two sorts of harmful effect:

- drugs may be prescribed in England that are not cost effective, because they have not been assessed by NICE
- uptake of cost effective drugs may be relatively low in England because of the so-called phenomenon of 'NICE blight' (that is, prescribers being reluctant to prescribe a drug that has not been assessed by NICE).

7.25 In relation to the first point, the absence of a NICE recommendation could lead to cost ineffective prescribing in England. As an indication of this, we estimated the cost in primary care in England of prescribing drugs that the SMC recommended against prescribing on all indications on cost effectiveness grounds. **In 2005, £47 million was spent on such drugs in England and over £55 million across the whole of the UK.**

7.26 It is more difficult to quantify 'NICE blight' (that is, the extent to which the absence of a NICE appraisal leads to low take up). However, the analysis conducted by NICE, companies and independent researchers, which was reviewed in Chapter 6, shows that there are many examples of drugs the uptake of which increased rapidly following a NICE appraisal. **It follows that for these drugs there would be a real benefit - for patients and companies - in securing an early-stage assessment.**

7.27 This issue – whether or all drugs should be assessed up front ('ex ante') – is one of the key design questions we consider in the assessment of options for reform in Annexe L.

### Ex post review of drugs

7.28 One of the most important issues we have identified is that under current arrangements there is no comprehensive mechanism for reviewing, over a given period, all drugs currently being prescribed.

7.29 Various factors can influence the cost effectiveness of a drug once it is on the market, such as updated clinical information on the drug in question (from new trials or observational studies from use in the community) or the effect of substitute products entering the market or going off patent. Conducting comprehensive ex post cost effectiveness reviews would allow such information to be captured in setting value-based prices for existing products, delivering value for money for the NHS.

- 7.30 Under current arrangements, existing drugs are not always subject to the same level of assessment as new drugs coming through the system. Several examples of this are discussed in Annexe M, which suggests that a number of products that are currently being prescribed in primary care are likely to be cost ineffective when compared against close therapeutic substitutes that have gone off patent.<sup>73</sup> These are in some cases very high revenue products, which can cost much more than available substitutes without offering significant additional benefits to patients.
- 7.31 While NICE does conduct some ex post reviews<sup>74</sup>, these sometimes focus on therapeutic groups rather than individual products. For example, the focus of NICE's review of statins published in 2006 was on the cost effectiveness of statins as a group (that is, relative to non-statin therapy) rather than on the cost effectiveness of individual statins relative to others. As noted above, TA94 did state 'it is recommended that therapy should usually be initiated with a drug with a low acquisition cost' but this is not as strong a signal as recommending against the use of a particular drug, for example. As discussed in Annexe M, one of the statins, atorvastatin, is the biggest selling drug in the NHS, and is almost ten times more expensive than simvastatin even though available evidence suggests there are no significant differences between the two in terms of clinical outcomes.
- 7.32 We recognise that moving towards a comprehensive system of ex post pricing reviews would be controversial for some stakeholders, notably certain companies, who would be concerned at the prospect of products that are already on the market being potentially subject to reviews against highly cost effective generics. But in our view, given the limited resources the NHS has at its disposal, it is vital that existing products be subject to the same cost effectiveness standards as new products coming onto the market. The alternative is neither efficient, nor, in our view, sustainable in the long run.
- 7.33 This issue has been thrown into stark relief in recent years with the increase in the number of new drugs – such as new treatments for cancer – that have been rejected by these bodies on cost effectiveness grounds.<sup>75</sup> Difficult choices are inevitable given the limited resources the NHS has at its disposal and we welcome the creation of bodies designed to maximise the use of those resources to meet patients' needs. But the existence of rationing underlines the need for the NHS to address any inefficiencies in current expenditure. A scheme that allowed the NHS to do so would be in the interests both of patients and of companies that are bringing new products onto the market.
- 7.34 We have heard concerns about the practicability of looking at all drugs on the market over a given period but, as noted in Annexe K, some countries are already doing this –

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<sup>73</sup> At the limit, if two drugs have entirely equivalent benefits for patients, then the ICER of the more expensive over the cheaper is, in effect, infinite. In practice the more expensive product is said to be 'dominated' by the cheaper and, under the processes of the bodies discussed here, would be rejected.

<sup>74</sup> For example, it reviews all Technology Appraisal guidance that it has previously issued.

<sup>75</sup> Rejections were at least partly on the basis of cost, with the uncertainty of clinical evidence also being a factor in some of the decisions. Some of the decisions are pending appeal. Chapter 10 of Annexe M gives some further details.

notably Sweden, which is currently in the process of assessing the cost effectiveness of all licensed medicines. Annexe L elaborates on specific pricing mechanisms that could incorporate ex post reviews of clinical and cost effectiveness, as a substitute for existing profit and price controls.

### **Institutional arrangements**

- 7.35 Companies we met in the course of this study expressed a range of views on the ways in which the different cost effectiveness bodies operated. This is unsurprising, given the different experiences companies have of the appraisal process and the different levels of success (in the form of positive recommendations) they enjoy. A broad consensus, such as there was one, was that NICE was felt to have the greatest technical expertise, while SMC and AWMSG have been particularly successful in establishing a collaborative approach with industry.
- 7.36 Companies and other stakeholders also expressed a number of views on how current institutional arrangements could be improved. We draw on these in the discussion below, which sets out how the institutional framework could be strengthened. These considerations apply to current arrangements, but are particularly important if the role of the bodies is increased under a value-based approach pricing.

### **Early engagement and dialogue**

- 7.37 Under current arrangements, NICE provides manufacturers with a scope that sets out what the drug appraisal will cover, the questions that need to be answered and the evidence needed to substantiate claims (including information on appropriate clinical endpoints and the implications for relevant costs and comparators). However, it has been argued that engagement with NICE and SMC comes too late in the day, when the companies in question have already completed their phase III trials.
- 7.38 Allowing for earlier engagement between the cost effectiveness bodies and companies (that is, at the phase III trials stage) will give companies a better opportunity to produce the sort of information that is needed to make a compelling case for the cost effectiveness of the drug. The recent Cooksey review has called for moves in the direction of earlier engagement and we welcome these proposals.
- 7.39 Constructive engagement and dialogue between companies and cost effectiveness bodies is clearly desirable at each subsequent stage of the assessment process, from submissions to appeals. A view that some companies have expressed to us – although, as noted, it is not possible to speak of a single 'industry view' – was that SMC has been particularly effective in adopting a genuinely collaborative approach. We draw on this experience in considering how to ensure open, constructive dialogue under any new pricing arrangements in Annexe L.

## **Efficiency in use of resources**

- 7.40 The final issue concerns the need to make the best use of available resources, implying a greater level of coordination than at present. Many companies feel that having to make cost effectiveness submissions to multiple bodies is not an efficient use of resources, particularly given the increasing overlap between SMC assessments and NICE STA appraisals. We recognise that this raises complex issues of sovereignty: the existence of multiple bodies represents a legitimate desire to have guidance and guidelines produced at a devolved level.
- 7.41 Pricing decisions are not devolved however. There are good reasons for this – multiple prices within the UK would lead to problems of parallel trade, creating supply side instability. UK-wide prices will remain a feature of any reformed pricing regime. This implies that, in producing cost effectiveness assessments as an input into a UK pricing decision, there will need to be greater coordination between the bodies.
- 7.42 In turn this will help meet the needs of making more efficient use of available HTA resources. Annexe L sets out some proposals for greater coordination and consistency of approach, distinguishing between medium and long term institutional arrangements. But it is important to note here that in both the short and long terms, we would envisage that existing institutions – NICE, SMC and AWMSG – would be retained, carrying out important functions on their own account within their countries of responsibility as well as providing coordinated inputs in UK-wide pricing decisions.
- 7.43 The approach we propose would also avoid the need for the time-consuming and resource-intensive process for selecting technologies for appraisal by NICE, since all products would be reviewed between the three bodies.

## **Principles and rules for assessing cost effectiveness and setting thresholds**

- 7.44 Companies and NHS stakeholders have expressed to us a number of views on matters of a more technical nature, relating to the rules for assessing the cost effectiveness of drugs.

### **Relevant costs and benefits**

- 7.45 We are sympathetic with many of these views, such as the idea that the notion of therapeutic value used by the bodies should embrace not just benefits to the patients themselves but to others who are affected by their condition, such as carers. In its assessments, NICE has made some moves in this direction and this is to be welcomed. Other views we find less compelling, such as the argument that the bodies should pay particular importance to the notion of innovation as a benefit in itself over and beyond value to patients. These issues would be as relevant under a reformed PPRS as they are under current arrangements and we evaluate them in some detail in Annexe L.

## The level of the threshold

- 7.46 One of the most important – and contentious – issues to address concerns the level of the threshold that should be applied to cost effectiveness assessments. Companies have said to us that greater clarity over the threshold would improve transparency, helping them manage the risks of investment. Some academic commentators have called for this as well.<sup>76</sup>
- 7.47 We would support this position in principle, while recognising that there may be situations in which the threshold may need to be adapted (for example, in accordance with the social value judgements discussed earlier in this annexe).<sup>77</sup> In cases where social value judgements heavily affect the outcome it is all the more important that the rationale behind decisions is clearly articulated and conveyed to health professionals, policy makers and the public. The general aspiration should be to be as explicit as possible about the principles and thresholds that will be applied in any given situation. The progress NICE in particular has made in this regard in recent years is encouraging.
- 7.48 Determining the level of the threshold is a particularly contentious issue, given the significant impact it has on NHS expenditure and companies' revenues. Given this, there is an argument that it is exposing the bodies to excessive pressure to expect them to develop an appropriate cost effectiveness threshold independently, without guidance or input from central Government.<sup>78</sup>
- 7.49 We believe there might be merit in an alternative system in which the level of the threshold – or indeed the level of the drug budget – were fixed for a period of time by central Government in consultation with industry. It could then be revised, perhaps as part of a renegotiation of reformed PPRS-style agreement, taking the place of current discussions about the level of the price cut and adjustments to the profit cap. We consider some of the principles and pieces of evidence that should be used to inform these periodic reviews in Annexe L. Retaining this role within central Government would become increasingly important under any system in which pricing and reimbursement decisions are delegated to an independent authority.

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<sup>76</sup> Raftery J. 'Review of NICE's recommendations, 1999-2005'. *BMJ*; 332, 2006.

<sup>77</sup> An alternative approach would be to adjust the estimate of QALYs produced to incorporate such factors rather than the threshold applied.

<sup>78</sup> The maximum cost / QALY threshold for all healthcare interventions could in principle be derived on a technocratic basis from the overall level of the NHS budget, which is one conception of what NICE attempts to do (see Culyer AJ, McCabe C, Briggs A, Claxton K, Buxton M, Akehurst R, Sculpher M, Brazier J. *Searching for a threshold, not setting one: the role of the National Institute of Health and Clinical Excellence* forthcoming, *Journal of Health Services Research and Policy*, 2007). However, setting the overall level of the NHS budget is a political decision. The point here – explored in greater detail in Annexe L – is that that, given the difficulty in deriving the correct threshold from overall NHS expenditure, there may be merit in reaching a political agreement – informed by relevant analysis – on the drugs component of budget (or maximum cost / QALY threshold applying to drugs).

## Conclusions

- 7.50 In the interests of patients, it is vital that NHS resources be used cost effectively. Since their creation, NICE, SMC and AWMSG have made a significant contribution to achieving this aim. They have also shown themselves able to adapt to changing needs – NICE's initiation of the STA process being a recent example.
- 7.51 We think there is a case for further reform, expanding the role of the bodies so that cost effectiveness assessment informs price setting directly, as a substitute for existing PPRS profit and price controls. Under such an arrangement, it is vital that rules for assessments are robust and that institutional arrangements work as well as possible. A transitional approach will also be required, to ensure capacity can be built up within the institutions. We have identified some issues to address to ensure this happens.
- 7.52 We recognise that this annexe has not gone into details as to the precise nature of the solutions and, in particular, what the specific role of NICE, SMC and AWMSG would be in the short and long term. These questions are addressed in Annexe L, which reviews options for reform.